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PHARMACEUTICAL PREFORMULATION: PHYSICOCHEMICAL PROPERTIES OF EXCIPIENTS AND POWDERS AND TABLET CHARACTERIZATION

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Contents

- 6.1.1 Introduction
- 6.1.2 Selection of Pharmaceutical Excipients
 - 6.1.2.1 Definitions and Goals
 - 6.1.2.2 Types of Pharmaceutical Excipients
 - 6.1.2.3 Characteristics of Pharmaceutical Excipients
 - 6.1.2.4 Selection Guideline of Pharmaceutical Excipients in Tablet Formulation
- 6.1.3 Drug–Excipient Compatibility
 - 6.1.3.1 Experimental Studies for Drug–Excipient Compatibility
 - 6.1.3.2 Analytical Methods for Drug–Excipient Compatibility
 - 6.1.3.3 Reaction Types and Stabilization Guidelines
- 6.1.4 Powder Characteristics
 - 6.1.4.1 Crystal Form and Habit
 - 6.1.4.2 Particle Size Distribution
 - 6.1.4.3 Flow Characteristics
 - 6.1.4.4 Density and Bulkiness
 - 6.1.4.5 Hygroscopicity
 - 6.1.4.6 Mixing
 - 6.1.4.7 Particle Size Reduction (Micronization and Milling)
 - 6.1.4.8 Compaction (Compressibility)
 - 6.1.4.9 Surface Area and Other Properties
- 6.1.5 Tablet Characterization
 - 6.1.5.1 Disintegration
 - 6.1.5.2 Dissolution

Pharmaceutical Manufacturing Handbook: Production and Processes, edited by Shayne Cox Gad
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- 6.1.5.3 Weight Variation
- 6.1.5.4 Hardness or Breaking Strength
- 6.1.5.5 Friability
- 6.1.5.6 Content Uniformity
- 6.1.5.7 Tablet Thickness
- 6.1.5.8 Tablet Shape and Size
- References

6.1.1 INTRODUCTION

Tablet is a major category of solid dosage forms which are widely used worldwide. Extensive information is required to prepare tablets with good quality at high standards. Based on preformulation studies, the optimal dosage forms are generally decided. When given orally, the solid dosage form tablet undergoes *in vitro* disintegration and dissolution followed by absorption through the gastrointestinal tract (GI). The *in vivo* biodistribution of drug which enters the systemic circulation then occurs (Figure 1).

In this section, general preformulation approaches for tablet production are described (Figure 2). The physicochemical properties of drug and excipients, which are crucial factors at the beginning stages, are presented. The types and functions of excipients used for tablet formulation and drug–excipient incompatibility are also discussed. Because tablets are prepared by compression of the drug with powdered excipients, the physicochemical properties of excipients and their multiple functions under regulatory standards are very important. To prepare a drug substance for the final dosage forms, pharmaceutical excipients should be added. The guidelines for selection of excipients are also given, based on the type and function of excipient, drug–excipient compatibility, type of tablet, and manufacturing parameters. Drug–excipient incompatibility is a very important issue before and after tablet preparation.

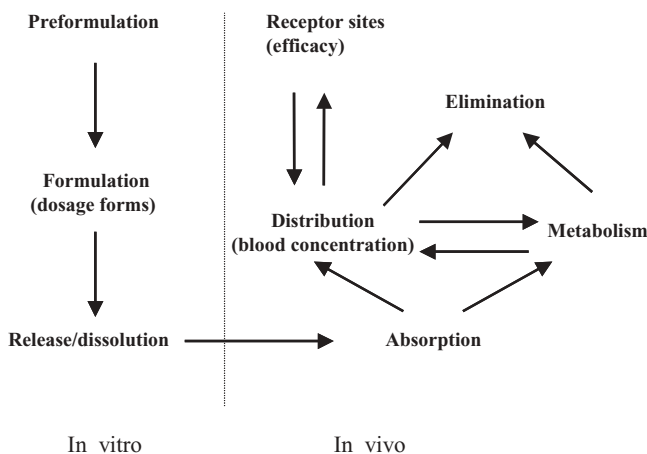


FIGURE 1 In vitro and in vivo pathways of drug which enters systemic circulation.

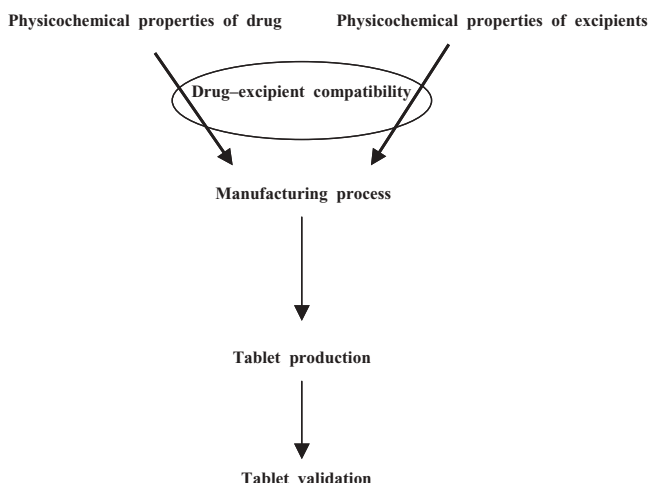


FIGURE 2 General preformulation approaches for tablet production.

tion. According to global International Conference on Harmonisation (ICH) guidelines, we should cautiously choose the excipients in tablet formulations because the quality and sources are variable by supplier and by batch.

In general, a tablet is prepared by mixing, milling, and compression the drug–excipient mixtures using a tablet machine. Therefore, powder characteristics of drug and excipients, including particle size, flow characteristics, bulk density, hygroscopicity, mixing and milling, and compaction, are extensively discussed. If these physical properties are not fully understood, tablets with good quality at high standards are often impossible to produce.

The prepared tablet must be validated according to regulatory guidelines. In general, disintegration, dissolution, friability, hardness, and weight are characterized for quality validation of finished tablet. This biopharmaceutical preformulation information for tablet production will guide us to design the optimal tablet very efficiently in the laboratory and industrial companies.

6.1.2 SELECTION OF PHARMACEUTICAL EXCIPIENTS

6.1.2.1 Definitions and Goals

A tablet contains active ingredients as well as other substances known as excipients, which have specific functions. The types and functions of various excipients which are incorporated into tablet formulations are discussed in many textbooks [1–3].

A pharmaceutical excipient is defined as an inactive ingredient or any component other than the active ingredient added intentionally to the medicinal formulation or everything in the formulation except the active drug. Pharmaceutical excipients are also called additives, pharmaceutical ingredients, or inactive pharmaceutical ingredients. There are many reasons for selecting and adding these pharmaceutical excipients in formulations. In the preparation of various dosage forms, it is essential to combine pharmaceutical excipients with model drugs as adjuvants to prepare the

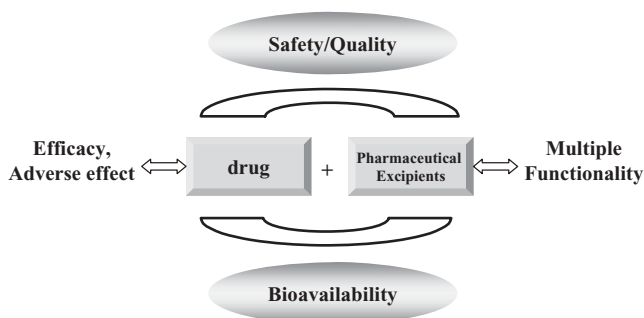


FIGURE 3 Correlation and functions of drug combined with pharmaceutical excipients in dosage form design.

solid dosage forms, mainly tablets. The pharmaceutical excipients make the drug into the final dosage forms. Physicochemical properties such as solubility, stability, metabolism, and even bioavailability of drugs can be varied by the pharmaceutical excipients [4–6]. Figure 3 shows the correlation and functions of drugs combined with pharmaceutical excipients in dosage form designs. Pharmaceutical excipients are regarded as key ingredients not only to decide optimal dosage forms but also to change the physicochemical and biological parameters of drugs. With an aid of pharmaceutical excipients, drug efficacy can be maintained. Changes of other types of dosage forms for different routes of administration are also achieved. The excipients can also function for the preparation of dosage formulation during the manufacturing processes. Patient compliance and modified releases of drugs can also be achieved if the excipients are properly applied. The colorant makes the tablet distinguishable after the coating process.

However, utilization of these pharmaceutical excipients is limited by the regulatory guidelines to be satisfied in the dosage formulations [3, 7]. In general, the regulatory guidelines require the following conditions for the use of excipients in the dosage formulations: (a) no harmful or toxicological effect and listed GRAS (generally recognized as safe), (b) good stability with no drug–excipient incompatibility and by any impurities in the excipients, (c) no interference in quality validation and analytical tests, (d) satisfaction of regulatory issues and guidelines in all countries where the product is to be marketed, (e) no instability with primary packing materials, (f) ease of accessibility, distribution, and economical cost, (g) satisfaction for environmental issues, (h) be physiologically inert, (i) be physically and chemically compatible with the active substance and the other excipients in the formulation, and (j) no unacceptable microbiological burden.

The *Handbook of Pharmaceutical Excipients* [1] contains some details of functional tests carried out on a wide range of excipients. The excipients all have pharmacopeial monographs, but it is important to understand that compliance with a monograph does not indicate equivalence between different grades or suppliers.

6.1.2.2 Types of Pharmaceutical Excipients

To prepare a drug substance into a final dosage form, pharmaceutical excipients should be added. The *Handbook of Pharmaceutical Excipients* presents more than

230 monographs of excipients used in the dosage formulations [1]. The amount and type of pharmaceutical excipients are highly dependent on the final dosage forms. In the preparation of tablets, diluents or fillers are commonly added to increase the bulk of the formulation, binders to cause the adhesion of the powdered drug and pharmaceutical substances, antiadherents or lubricants to assist in the smooth tabletting process, disintegrating agents to promote tablet break-up after administration, and coating agents to improve stability, control disintegration, or enhance appearance. Thus, the pharmaceutical excipients establish the primary features and physicochemical properties of the tablet, such as the physical form, stability, dissolution, taste, and overall appearance [3]. Table 1 presents examples of pharmaceutical excipients used in tablet formulations according to principal categories.

6.1.2.3 Characteristics of Pharmaceutical Excipients

Filler (Diluent) Powder mixtures should be compacted to achieve the appropriate strength at a low compaction pressure in the tablet preparation. The compaction properties of a formulation will largely be governed by its major components. For a high-dose drug the drug itself will strongly influence the compaction, while for low-dose drugs the bulk size needs to be increased with an inactive ingredient

TABLE 1 Pharmaceutical Excipients Used in Tablet Formulations

Excipient Type	Definition	Examples
Adsorbent	Agent capable of holding other molecules onto its surface by physical or chemical (chemisorption) means	Powdered cellulose, activated charcoal
Antioxidant	Agent that inhibits oxidation and thus is used to prevent deterioration of preparations by oxidative process	Ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde, sulfoxylate, sodium metabisulfite
Colorant	Used to impart color to tablet	FD&C red no. 3, no. 20, FD&C yellow no. 6, FD&C blue no. 2, D&C green no. 5, D&C orange no. 5, D&C red no. 8, caramel, ferric oxide, red
Encapsulant	Used to form thin shells for purpose of enclosing drug substance or drug formulation for ease of administration	Gelatin, cellulose acetate phthalate
Plasticizer	Used as component of film coating solutions to enhance spread of coat over tablets, beads, and granules	Diethyl phthalate, glycerin

TABLE 1 *Continued*

Excipient Type	Definition	Examples
Surfactant	Substance that adsorbs to surfaces or interfaces to reduce surface or interfacial tension; may be used as wetting agent, detergent, or emulsifying agents	Benzalkonium chloride, nonoxynol 10, octoxynol 9, polysorbate 80, sodium lauryl sulfate, sorbitan monopalmitate
Tablet antiadherent	Agent that prevents the sticking of tablet formulation ingredients to punches and dies during tablet production	Magnesium stearate, talc
Tablet binder	Substance used to cause adhesion of powder particles in tablet granulations	Acacia, alginic acid, carboxymethylcellulose sodium compressible sugar, ethylcellulose gelatin, liquid glucose, methylcellulose povidone, pregelatinized starch
Tablet diluent	Inert substance used as filler to create desired bulk, flow properties, and compression characteristics in preparation of tablets	Dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sorbitol, starch
Tablet sugar and film coating excipient	Used to coat a formed tablet for purpose of protecting against drug decomposition by atmospheric oxygen or humidity, to provide desired release pattern for drug substance after administration, to mask taste or odor of drug substance, or for aesthetic purposes	Sugar: liquid glucose, sucrose Film: hydroxyethyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose Enteric: cellulose acetate phthalate, shellac (35% in alcohol)
Tablet direct-compression excipient	Used in direct-compression tablet formulations	Dibasic calcium phosphate
Tablet disintegrant	Used in solid dosage forms to promote disruption of solid mass into smaller particles which are more readily dispersed or dissolved	Alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate, starch
Tablet glidant	Agent used in tablet and capsule formulations to improve flow properties of powder mixture	Colloidal silica, corn starch, talc
Tablet lubricant	Substance used in tablet formulations to reduce friction during tablet compression	Calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc stearate
Tablet opaquant	Used to render tablet coating opaque; may be used alone or in combination with colorant	Titanium dioxide
Tablet-polishing agent	Used to impart an attractive sheen to coated tablets	Carnauba wax, white wax

TABLE 2 Commonly Used Tablet Diluents

Diluent	Comments
Lactose	Available as anhydrous and monohydrate; anhydrous material used for direct compression due to superior compressibility
Microcrystalline cellulose	Originally direct-compression excipient, now often included in granulations due to its excellent compressibility
Dextrose, glucose	Direct-compression diluent, often used in chewable tablets
Sucrose	Was widely used as sweetener/filler in effervescent tablets and chewable tablets; less popular nowadays due to cariogenicity
Starch and derivatives	Versatile material that can be used as diluent binder, and disintegrant
Calcium carbonate	Brittle material
Dicalcium phosphate	Excellent flow properties; brittle material
Magnesium carbonate	Direct-compression diluent

termed a diluent (or filler). High-dose formulations may also use a diluent to overcome compaction problems experienced with an active pharmaceutical substance.

There are a number of general rules for selecting a diluent. The selection of the diluent will depend on the type of processing and plasticity of materials to be used. A direct-compression formulation will require a diluent with good flow and compaction properties. If the material is extremely plastic, it is appropriated to add a diluent that compacts by brittle fracture; similarly, a brittle drug substance should be combined with a plastic filler. The solubility of the drug substance should also be considered. A soluble drug is normally formulated with an insoluble filler to optimize the disintegration and dissolution process. The hydrophilic excipients added in the formulation may also change drug solubility. Table 2 lists the more commonly used diluents in tablet formulation.

Binder (Granulating Agent) Before tableting the powder mixture via direct compression, generally powders are granulated simply by adding water or an organic solvent to form liquid bridges followed by the drying process. This granulation process can make powders of larger particle size and that are more free flowing for tablet production. The most common method of adding binders is as a solution in the granulating fluid. It is also possible add synthetic polymers such as PVP and HPMC as powders and use water as the granulating agent. When the granulate dries, the crystallization of any solids that had dissolved in the liquid will form solid bonds between the particles [8]. Inclusion of granulating agents or binders to increase granule strength is necessary. Granulating agents are usually hydrophilic polymers that have cohesive properties that both aid the granulation process and impart strength to the dried granulate.

For a granulating agent to be effective, it must form a film on the particle surface and be selected on the basis of its spreading coefficient. The spreading coefficient is defined as the difference between the *work of adhesion* of the binder and the substrate and the *work of cohesion* of the binder. Commonly used granulating agents are listed in Table 3. The binder may vary the disintegration and dissolution. Binders form hydrophilic films on the surface of the granules, which can aid in the

TABLE 3 Commonly Used Granulating (Binding) Agents

Granulating Agent	Normal Concentration (%)	Comments
Starch	5–25	Was once the most commonly used binder; starch has to be prepared as paste, which is time consuming
Pregelatinized starch	0.1–0.5	Cold-water soluble so easier to prepare than starch
Acacia	1–5	Requires preparation of past prior to use; can lead to prolonged disintegration times if used at too high a concentration
Polyvinylpyrrolidone (PVP)	2–8	Available in range of molecular weight/viscosities; soluble in water and ethanol
Hydroxypropyl methylcellulose (HPMC)	2–8	Low-viscosity grades most widely used
Methylcellulose (MC)	1–5	—

wetting of hydrophobic drugs. However, if added at too great concentrations, the films can form viscous gels on the granule surface and will retard dissolution.

Disintegrant Tablets must have sufficient strength to withstand the stresses of subsequent manufacturing operations, such as the coating, packaging, and distribution process. However, once the tablet is taken by the patient, it must break up rapidly to ensure rapid dissolution of the active ingredient in immediate-release preparations. To overcome the cohesive strength produced by the compression process and to break down the tablet into the primary particles as rapidly as possible, the disintegrants are combined with other excipients during the tableting process. Starch was the first disintegrant used in tablet manufacture. Recently, so-called superdisintegrants, including croscarmellose sodium, sodium starch glycolate, and crospovidone, display excellent disintegration activity at low concentrations and have better compression properties than starches. Traditionally, swelling and rate of swelling have been regarded as the most important characteristics of disintegrants. With the aid of these superdisintegrants, sustained-release acetaminophen tablets with biphasic patterns were successfully established to mimic the bilayered Tylenol ER tablet [9]. As a general rule, soluble drugs are formulated with insoluble fillers to maximize the effect of disintegrants. The positioning of disintegrants within the intragranular and extragranular portions of granulated formulations can affect their water uptake and disintegration time.

Commonly used disintegrants are listed in Table 4. The greater the level of disintegrant, the faster the tablet will disintegrate. The compaction properties of many disintegrants, including starch, are not satisfactory and use of high concentration could also reduce tablet strength. Disintegrants are hygroscopic materials and will absorb moisture from the atmosphere, which could negatively affect the stability of moisture-sensitive drugs if the packaging does not provide adequate protection from the environment. Disintegrant activity can be affected by mixing with hydrophobic lubricants so that care needs to be taken to optimize the manufacturing

TABLE 4 Commonly Used Disintegrants

Disintegrant	Normal Concentration (%)	Comments
Starch	5–10	Probably works by wicking; swelling minimal at body temperature
Microcrystalline cellulose		Strong wicking action; loses disintegrant action when highly compressed
Insoluble ion exchange resins		Strong wicking tendencies with some swelling action
Sodium starch glycolate ^a	2–8	Free-flowing powder that swells rapidly on contact with water
Croscarmellose sodium ^a	1–5	Swells on contact with water
Gums—agar, guar, xanthan	<5	Swell on contact with water; form viscous gels that can retard dissolution, thus limiting concentration that can be used
Alginic acid, sodium alginate	4–6	Swell like gums but form less viscous gels
Crospovidone ^a	1–5	High wicking activity

^aOften mentioned as superdisintegrant.

process as well as the formulation. If the tablet contains a high proportion of a hydrophobic drug that has a high contact angle, a wetting agent or surfactant should be added to the formulation to modify disintegration time and subsequent dissolution of the drug from tablet. The most commonly used wetting agents are sodium lauryl sulfate and the polysorbates.

Most pharmacopeias include a disintegration test which can be applied to tablets and capsules and the detailed monograph is given in the pharmacopeias (see Section 6.1.5.1).

Lubricant The use of a lubricant is essential to increase the free flow of powders and to prevent manufacturing disorders in the tablet production. The type and amount of lubricant are cautiously selected in the formulation. The order of addition and mixing time is also considered in the tableting process.

There are three types of lubricants employed in solid dosage form manufacture. The first class of lubricant is the *glidant*. The flow properties of a powder can be enhanced by the inclusion of a glidant. These are added to overcome powder cohesiveness. The two other classes of lubricant are *antiadherent* excipients, which reduce the friction between the tablet punch faces and tablet punches, and *die wall lubricant* excipients, which reduce the friction between the tablet surface and the die wall during and after compaction to enable easy ejection of the tablet. The level of a lubricant required in a tablet is formulation dependent and can be optimized using an instrumented tableting machine.

Commonly used lubricants are listed in Table 5. Talc is traditionally one of the most commonly used glidants, having the additional benefit of being an excellent antiadherent. The level of talc that can be added to a formulation is restricted by its hydrophobic nature, too high levels resulting in decreased wetting of the tablet and a subsequent reduction in the rate of dissolution. Fumed silicon dioxides are

TABLE 5 Lubricants Commonly Used in Formulations

Lubricant	Typical Percent	Comments
<i>Glidants</i>		
Talc	1–5	Fine, crystalline powder; Widely used as lubricant and diluent
Fumed silicon dioxide: Aerosil, Cab-O-Sil, Syloid	0.1–0.5	Has small particle size and large surface area for good flowability; used for adsorbent, antitacking agent disintegrant, and glidant
Starch	1–10	Mainly used for binder, disintegrant, and diluent but also used for glidant
Sodium lauryl sulfate	0.2–2	Anionic surfactant, lubricant and wetting agent
<i>Boundary Lubricants</i>		
Magnesium stearate	0.2–2	Hydrophobic, variable properties between suppliers
Calcium silicate	0.5–4	Hydrophobic
Sodium stearyl fumarate	0.5–2	Less hydrophobic than metallic stearates, partially soluble
Polyethylene glycol 4000 and 6000	2–20	Soluble, poorer lubricant activity than fatty acid ester salts
Sodium lauryl sulfate	1–3	Soluble, also acts as wetting agent
Magnesium lauryl sulfate	1–3	Acts as wetting agent
Sodium benzoate	2–5	Soluble
<i>Fluid Lubricants</i>		
Light mineral oil	1–3	Hydrophobic, can be applied to either formulation or tooling
Hydrogenated vegetable oil	1–5	Hydrophobic, used at higher concentrations as controlled-release agents
Stearic acid	0.25–2	Hydrophobic
Glyceryl behenate	0.5–4	Hydrophobic, also used as controlled-release agent

perhaps the most effective glidants. These are materials with very small (10-nm) spherical particles that may achieve their glidant properties. They are available in a number of grades with a range of hydrophobic and hydrophilic forms and also commercially available under diverse brand names. Starch has also been used as a glidant. The use of large amounts of starch has also aided the disintegration properties.

Die-wall lubricants can be divided into two classes, *fluid and boundary lubricants*. Fluid lubricants work by separating moving surfaces completely with a layer of lubricant. These are typically mineral oils or vegetable oils, and they may be either added to the mix or applied directly to the die wall by means of wicked punches. The oily lubricants may have a mottled appearance in the tablet due to uneven distribution, poor powder flow due to their tacky nature, and reduced tablet strength. Fluid lubricants include stearic acid, mineral oils, hydrogenated vegetable oils, glyceryl behenate, paraffins, and waxes. Boundary lubricants work by forming a thin solid film at the interface of the die and the tablet. Metallic stearates are the most

widely used boundary lubricants. Such lubricants should have low shear strength and form interparticulate films.

Magnesium stearate is the most widely used lubricant. The magnesium stearate used in the pharmaceutical industry is not a pure substance but a mixture of magnesium salts of fatty acids, though predominantly magnesium stearate and magnesium palmitate. Despite its popularity, which is a reflection of its excellent lubricant properties, it has some problems associated with product consistency: its effect on tablet strength and its hydrophobicity. The U.S. Pharmacopeia (USP) requires that the stearate content should account for not less than 40% of the fatty acid content of the material, and the stearate and palmitate combined should account for not less than 90%. Within this definition, there are a range of materials to be supplied as magnesium stearate. For a given formulation, it is important that a single source of magnesium stearate be used for all batches to get product reliability.

The lubricant activity of magnesium stearate is related to its readiness to form films on the die wall surface. As a result, it has two consequences: a reduction in the ability of the powder to form strong compacts and, due to its hydrophobicity, a deleterious effect on the dissolution rate of the tablets. The hydrophobic surfaces created by magnesium stearate have been shown to reduce the rate of dissolution and bioavailability of several tablet formulations. When both lubricant and disintegrant are being added to a granulated formulation, the disintegrant should be blended with the granules prior to the addition of the lubricant to minimize the risk of forming a hydrophobic film around the disintegrant.

The third class of lubricant activity is the antiadherent. Some materials have adhesive properties and can adhere to the punch surfaces during compression. This will induce tablet disorders: sticking, with a film forming on the surface of the tablets, or picking, where solid particles from the tablet stick to the punch surface. Most die wall lubricants also have antiadherent actions, and in many formulations, the addition of a specific antiadherent will not be required separately. The antiadherent includes talc, maize starch, and microcrystalline cellulose.

Coating Materials The core compressed tablet can be used by itself, but an additional coating process of the compressed tablet can be applied for several reasons: (a) protection of the drug from the environment (moisture, air, light) for stability reasons, (b) taste masking, (c) minimizing patient/operator contact with drug substance, particularly for skin sensitizers, (d) improving product identity and appearance, (e) improving ease of swallowing, (f) improving mechanical resistance and reducing abrasion and attrition during handling, and mostly (g) modifying release properties.

There are three main methods used to coat pharmaceutical tablets: *sugar coating*, *film coating*, and *compression coating*. Sugar coating has been the most commonly used method and involves coating tablets with sucrose. A sugar-coated tablet is water based and generally starts to break up in the stomach. This is a highly skilled and multistep process that is very labour intensive. This coating process results in a 50% increase of the final tablet weight and in a significant increase in tablet size. Traditionally, sugar coating has been performed in coating pans in which the tablets are tumbled in a three-dimensional direction. The pan is supplied with a source of warm air for drying and an extraction system to remove moist air and dust. The coating solution is distributed around the tablets by their tumbling action. A dusting

powder may be sprinkled onto the surface of the tablets during the drying phase to prevent the tablets from sticking together. The cycle of wetting and drying is continued until the desired amount of coating has been applied to the tablets. Typically, a sugar coating will consist of three types of coats: a sealing coat, a subcoat, and a smoothing coat. Traditionally, a seal coating of shellac dissolved in ethanol or synthetic water-resistant polymers such as cellulose acetate phthalate or polyvinylacetate phthalate is used. The subcoat is an adhesive coat on which the smoothing coat of the sharp corners of the tablet can be built. The subcoat is a mixture of a sucrose solution and an adhesive gum, such as acacia or gelatin, which rapidly distributes over the tablet surface. A dusting follows each application of solution with a subcoat powder containing materials such as calcium carbonate, calcium sulfate, acacia, talc, and kaolin. The smoothing coat consists of the majority of the tablet bulk and provides the tablet with a smooth finish. A colorant is also applied if needed. The coat consists of sucrose syrup which may contain starch or calcium carbonate. The coated tablets are usually transferred to a polishing pan and coated with a beeswax–carnauba wax mixture to provide a glossy finish to the surface.

Film coating involves the application of a polymer film to the surface of the tablet, gelatin capsules, and multiparticulate systems with a negligible increase in tablet size. The method of application of the coat differs from the sugar coating in that the coating suspension is sprayed directly onto the surface of the tablets, and drying occurs as soon as the coat hits the tablet surface. The tablet only receives a small quantity of coating solution at a time. The film coat can generally be affected by the following properties: a method of atomizing the coating suspension, the ability to heat large volumes of air (which heat the tablets and facilitate the rapid drying of the applied coat), and a method of moving the tablets that ensures all tablets are evenly sprayed.

The main methods of coating are modified conventional coating pans, side-vented pans, and fluid bed coating. The side-vented pan, now the most commonly used equipment for film coating, was designed to maximize the interaction between the tablet bed and the drying air. The mixing efficiency of the table, granules, or pellets is achieved by using appropriately designed baffles on the pan surface. Fluid-bed coating offers an alternative to pan coating and is particularly popular for coating multiparticulate systems. There are three methods by which the coating can be applied: top spraying, bottom spraying, and tangential coating. The pellets, granules, or tablets being coated are suspended in an upward stream of air, maximizing the surface available for coating. The coating is applied by an atomizer, and this is dried by the fluidizing air.

Table 6 gives commonly used polymers for film coating of core tablet. With the exception of HPMC, the polymers are rarely used alone but are combined with other polymers to optimize the film-forming properties. A polymer for film coating will ideally meet the following criteria:

1. Solubility in the solvent selected for application: Currently the organic solvent are replaced with water as a suspension system, although certain types of film coatings may require organic solvents to be used. Commonly used solvents include alcohols (methanol, ethanol, and isopropanol), esters (ethyl acetate and ethyl lactate), ketones (acetone), and chlorinated hydrocarbons (dichloromethane and trichloroethane).

TABLE 6 Commonly Used Polymers for Film Coating of Core Tablet

Polymer	Comments
Methylcellulose (MC)	Soluble in cold water, GI fluids, and a range of organic solvents
Ethylcellulose (EC)	Soluble in organic solvents, insoluble in water and GI fluids; used alone in modified-release formulations and in combination with water-soluble cellulose for immediate-release formulations
Hydroxyethylcellulose (HEC)	Soluble in water and GI fluids
Methyl hydroxyethylcellulose (MHEC)	Soluble in water and GI fluids; has similar film-forming properties to HPMC but is less soluble in organic solvents, which limited its popularity when solvent coating was the norm
Hydroxypropyl cellulose (HPC)	Soluble in cold water, GI fluids, and polar solvents; becomes tacky when dried, so is unsuitable for use alone, often used in combination with other polymers to optimize adhesion of coat
Hydroxypropyl methylcellulose (HPMC)	Soluble in cold water, GI fluids, alcohols, and halogenated hydrocarbons; excellent film former and the most widely used polymer; can be used with lactose to improve adhesiveness
Sodium carboxymethylcellulose (NaCMC)	Soluble in water and polar solvents

2. Solubility in GI fluids: The solubility of polymers is dependent on its physico-chemical nature and pH. Unless the coating is being applied for enteric coating, it should ideally be soluble across the range of pH values encountered in the GI tract.
3. Capacity to produce an elegant film even in the presence of additives such as plasticizers, pigments, and colorants.
4. Compatibility with film-coating additives and the tablet being coated.
5. Stability in the environment under normal storage conditions.
6. Freedom from undesirable taste or odor.
7. Lack of toxicity.

Enteric coating materials are also used to prevent release of the drug substance in the stomach if the drug is either an irritant to the gastric mucosa or unstable in gastric juice. Table 7 lists enteric coating polymers commonly used in tablet formulations. The choice of enteric coating material depends on its solubility.

The third type of tablet coating is multiple-compression coating to make a bilayered, multilayered tablet (a layered tablet of two drugs) or a tablet within a tablet (a core of one drug and a shell of another). The multilayered tablet is prepared by initial compaction of a portion of the fill materials in a die followed by additional fill material and compression, depending on the number of fill materials. The layered tablet can provide some advantages. Each layer has different drug in a separate layer. The incompatible drug can be compressed simultaneously at different layers.

TABLE 7 Enteric Coating Polymers Commonly Used in Tablet Formulations

Polymer	Solubility Profile	Comments
Shellac	Above pH 7	Original enteric coating material, originally used in sugar-coated tablets; high pH required for dissolution may delay drug release; natural product which exhibits batch-to-batch variability
Cellulose acetate phthalate (CAP)	Above pH 6	High pH required for dissolution a disadvantage; forms brittle films, so must be combined with other polymers
Polyvinylacetate phthalate (PVAP)	Above pH 5	—
Hydroxypropyl methylcellulose phthalate (HPMCP)	Above pH 4.5	Optimal dissolution profile for enteric coating
Polymers of methacrylic acid and its esters	Various grades available with dissolution occurring above pH 6	—

The staged release and improved appearance from the layered tablet are also possible. In the preparation of a tablet within a tablet, a special tableting machine is required to place the intended core tablet precisely within the die, which already contains some of the coating formulation to surround the fill materials. This multi-layered tablet or tablet within a tablet is also useful to get the modified release, either immediately or in a sustained manner.

Auxiliary Excipients Plasticizers are added during the tablet coating process. The film coating process involves two important stages: droplet formation and film formation. Film formation is a multistage process that involves wetting the tablet surface followed by spreading the film and eventually coalescence of the individual film particles into a continuous film. Most film-forming polymers have glass transition temperatures in excess of the temperatures reached during the coating process (typically 40–50 °C), so it is necessary to add plasticizers to the formulations which reduce the glass transition temperature. The choice of plasticizer is dependent on the type of polymer and its permanence and compatibility. Permanence is the duration of the plasticizer effect; the plasticizer should remain within the polymer film to retain its effect, so it should have a low vapor pressure and diffusion rate. Compatibility requires the plasticizer to be miscible with the polymer. Commonly used plasticizers include phthalate esters, citrate esters, triacetin, propylene glycol, polyethylene glycols (PEGs), and glycerol.

The pigments or opacifiers are also combined with the coating solution to get colored tablets. Insoluble pigments are normally preferred to soluble dyes for a number of reasons. Solid pigments produce a more opaque coat than dyes, protecting the tablet from light. The presence of insoluble particles in the suspension allows

the rate of solid application to the tablet to be increased without having an adverse effect on the viscosity of the coating suspension, improving productivity.

6.1.2.4 Selection Guideline of Pharmaceutical Excipients in Tablet Formulation

In the proper selection of pharmaceutical excipients for the formulation, there are numerous factors to be considered [7]. The type of excipient is highly dependent on the model compound and its intended dosage form. The preparation method of the dosage form and proper dosage regime are also factors.

The formulation parameters of the tablet are essential. The amount and type of excipients relative to drug contents should be considered to determine the size of the dosage form. The bulk density of excipients and drug and their filling doses in the die are important factors to be considered in the tablet formulation. Uniform distribution of drug or excipient is in trouble if its contents are low in the formulation, while the use of high contents are difficult to fill in the die and the tablet size is also larger. Excipients that are potentially incompatible with the drug should be avoided. The amount and type of reactive impurities in the excipients should also be established. Batch-to-batch and supplier-to-supplier variation in impurity levels is possible. Excipients with potential adverse interaction and any unwanted incompatibility with drug should be avoided in the formulation. For an ideal formulation, it is helpful to consider these parameters as well as drug–excipient incompatibility.

The global harmonization and standardization of pharmaceutical excipients are nowadays necessary in the formulation studies [3, 7]. Since all excipients in the market worldwide are supplied from many countries or companies with facilities in more than a single country, the quality of the excipients must be well documented and validated. Otherwise, the quality of the excipients should be varied batch to batch, factory to factory, and country to country. There are also hundreds of different brands and grades of excipients available, but it would be unrealistic for the formulator to expect to have a totally free choice. Most manufacturing companies select the excipients used in their factory on the basis of cost, availability, and performance. To establish the equivalency of excipients obtained from different sources, it is also necessary to perform some kind of functionality testing. Since the sources, origin, and manufacturer of the excipients are different, regulatory approval for the product is required in each country. The standards for each drug substance and excipient are contained in pharmacopeia. The four pharmacopeia with the largest international use are the United States Pharmacopeia (USP) and National Formulary (NF), British Pharmacopoeia (BP), European Pharmacopoeia (EP), and Japanese Pharmacopoeia (JP).

Unless global harmonization is established, analytical methods, testing criteria, and specification limits must be variable according to monographs of pharmacopeia from the different countries. For example, Table 8 lists the different specification limits for the viscosity of cellulose ether among three pharmacopeias. If global harmonization and standardization of pharmaceutical excipients are established, the marketing and sales of a single formulation are more facilitated worldwide. The manufacturing cost and research-and-development (R&D) cycles are also reduced. Most of all, the quality and bioequivalence of the drug products with the same formulation can be more validated since the regulatory approval of the pharmaceutical product is enhanced. The global harmonization is an ongoing effort by corporate representatives and international regulatory authorities.

TABLE 8 Specification Limits for Viscosity of Cellulose Ether

Parameter	EP	USP XXII	JP XII
Concentration of solution, %	2.0	2.0	2.0
Temperature, °C	20 ± 0.1	20 ± 0.1	20 ± 0.1
Type of viscometer	Rotating viscometer	Capillary type, Ubbelohde	Capillary type, Ubbelohde
Shear rate, S ⁻¹	10	—	—
Unit	cP (Pa·s)	cP (Pa·s)	cSt
Sample preparation ^a			

^aVery similar in all three pharmacopeia.**TABLE 9 Comparative Properties of Some Directly Compressible Fillers^a**

Filler	Compactibility	Flowability	Solubility	Disintegration	Hygroscopicity	Lubricity	Stability
Dextrose	3	2	4	2	1	2	3
Spray dried lactose	3	5	4	3	1	2	4
Fast-Flo lactose	4	4	4	4	1	2	4
Anhydrous lactose	2	3	4	4	5	2	4
Emdex (dextrans)	5	4	5	3	1	2	3
Sucrose	4	3	5	4	4	1	4
Starch	2	1	0	4	3	3	3
Starch 1500	3	2	2	4	3	2	4
Dicalcium phosphate	3	4	1	2	1	2	5
Avicel (MCC)	5	1	0	2	2	4	5

^aGraded on a scale from 5 (good/high) to 1 (poor/low); 0 means none.

In the selection of excipients, formulation scientists should also remember that every excipient is not limited by a single function but rather can be used for many pharmaceutical applications in dosage forms. For example, cellulose and its derivatives (HPMC, EC, HPC) have been widely used as fillers, binders, suspending agents, and mainly controlled-release agents. Povidone, polymethacrylate, and cyclodextrins are also multifunctional excipients in formulations. Table 9 gives the physical properties of some directly compressible fillers. The grades of physical properties are variable among fillers used in tablet formulation. The simple and optimal formulation of drugs with multifunctional excipients can provide some advantages in tablet preparations.

6.1.3 DRUG-EXCIPIENT COMPATIBILITY

The potential for excipients to cause chemical and physical instability in drugs has been recognized for over 30 years. Drug compatibility studies have been used as an

approach for accepting/rejecting excipients for use in pharmaceutical formulations [1, 10–12]. In general, drug stability can be investigated under the stress condition according to the guideline of accelerated stability testing. The factors for stress condition usually include temperature, pH, light, moisture, agitation, gravity, packaging, and method of manufacture [13, 14]. Despite this fact, approaches for excipient selection in drug formulation are often empirical. The stability issues in the development of a drug must be considered at the early and late formulation stages. Nowadays, advanced analytical instrumentation makes it possible to more rapidly identify potential excipient-induced instability to select excipients. Excipients that exhibit incompatibility with the drug are “rejected” and not included in subsequent tablet formulation studies.

6.1.3.1 Experimental Studies for Drug–Excipients Compatibility

Compatibility studies are carried out by mixing drug with one or more excipients under some type of stress condition. It has also been suggested that aqueous suspensions of the drug and excipients or drug–excipient complexes provide a better model for tablet formulations. It has been recommended that small-scale formulations using the selected excipients (this may eventually be used for the eventual formulation) be prepared using experimental processes.

Table 10 provides examples of binary and factorial design for drug–excipient compatibility studies. The two conditions of each potential parameter can be included as a binary system. All potential parameters can also be combined for factorial design. For example, water is added to the drug–excipient mixture at reasonable temperatures (50 °C or less) and then both intact drug and degradation products are measured. The high-temperature and high-humidity conditions are usually used to obtain more rapid stability assessment of drug and excipients. Generally, physicochemical properties such as drug content, color, taste, related substances, thermal analysis, and high-performance liquid chromatography (PLC) studies of evaluated for drug–excipient compatibility studies using conventional analytical techniques.

6.1.3.2 Analytical Methods for Drug–Excipient Incompatibility

The key to the early assessment of instability in formulations is the availability of analytical methods to detect low levels of degradation products, generally less than 2%. With the aid of thermal analysis and chromatographic methods [HPLC and

TABLE 10 Examples of Binary and Factorial Designs for Drug–Excipient Compatibility Studies

Binary Design	Factorial Design
Drug–excipient ratio 1:1 or 1:10	Total number of formulation = $a \times b \times c \times d \times e$
Water addition = yes/no	Type of drug–excipient (<i>a</i>)
Storing temperature 25 °C or 40 °C/75%	Amount of drug–excipient (<i>b</i>)
Storing time 1 or 4 weeks	Water addition (<i>c</i>)
	Storing temperature (<i>d</i>)
	Storing time (<i>e</i>)

liquid chromatography/mass spectrometry (LC/MS)], it can assign at least tentative structures for most degradation products as well as the intact drug contents [15]. Excipient compatibility screening must provide more rapid identification of excipient-mediated instability that is detected in complete formulations.

Early compatibility studies relied on color change as an indication of incompatibility. Subsequently, there were numerous reports on the use of thermal analysis techniques such as differential thermal analysis (DTA) or differential scanning calorimetry (DSC) to detect drug–excipient incompatibilities. DTA and DSC have the advantage of rapid analysis. Generally, formation of new peaks and disappearance of drug peak by the endothermic or exothermic reaction are carefully investigated. Diffuse reflectance spectroscopy (DRS) can be also used to determine the ultraviolet (UV) absorption of drug on the surface of drug–excipient mixtures.

6.1.3.3 Reaction Types and Stabilization Guidelines

Understanding the degradation chemistry of drug with excipients is essential to select proper excipients in the formulation stages [16, pp 101–151]. Drug–excipient compatibility studies are crucial to decide optimal tablet formulation and to understand the possible mechanism in many cases [10, 12, 14]. Drug instability occurs by three types of reactions: hydrolysis, oxidation, and aldehyde–amine addition. Table 11 gives reaction types of chemical and physical instability.

Hydrolysis is the most common mechanism to induce drug–excipient incompatibility. Most hydrolysis reactions are catalyzed by acids and/or bases. The microscopic pH between drug and excipients is critical. The pH degradation rate profiles are good predictors for hydrolysis reactions in solid dosage forms. The pH of optimal stability in solution is similar to the “microscopic pH” in solid dosage forms. A shift

TABLE 11 Reaction Types of Chemical and Physical Instability

Type of Instability	Order of Frequency
Chemical instability	
pH-dependent hydrolysis	12
Oxidation	
Air oxidation	5
Metal-catalyzed oxidation	3
Peroxides in excipients	2
Aldehyde–amine addition	
Aldose excipient	2
Formaldehyde from excipients	1
Michael addition with maleate salt	1
Intramolecular cyclization	1
Dimerization (Diels–Alder)	1
Racemization	1
Addition of ammonia residue from gelatin capsule	1
Esterification	1
Physical instability	
Evaporation of volatile free base	2
Reaction of methanesulfonic acid with disintegrants	1
Gelatin cross-linking by excipient impurities	1

in only one pH unit can increase or decrease the reaction rate by a factor of 10. Although solid-state compatibility studies are commonly used, solution kinetic studies are generally conducted to select excipients since it is possible to study all three of these reactions in solution. Often solution kinetic studies allow the identification of more potential degradation products and hence the development of better stability-indicating assays. The pH of optimal stability is also important for selecting the appropriate salt form of the compound and excipients in the solid formulation. Acetylsalicylic acid (ASA) is a readily hydrolyzable drug and there are literature references to its rate of hydrolysis in aqueous solution.

The moisture content of the drug and excipients plays a critical role in their incompatibility by hydrolysis. Excipients such as starch and povidone have particularly high water contents (povidone contains about 28% equilibrium moisture at 75% relative humidity), which can increase the possibility of drug contact. Magnesium trisilicate causes increased hydrolysis of aspirin in tablet form because, it is thought, of its high water content. For these reasons, some scientists recommend inclusion of water in the samples for compatibility studies. Depending on the degree of hydrolytic susceptibility, different approaches for tablet formulation can be used to minimize hydrolysis. For compounds such as ASA that are readily hydrolyzable, direct compression or dry granulation is preferable rather than wet granulation. However, drug-exciipient incompatibility still occurs. Chemical interaction between moieties of drug and excipients may lead to increased decomposition. The trans-acetylation reaction between aspirin and paracetamol and also possible direct hydrolysis of the paracetamol can occur. The amount of free salicylic acid at 37°C in the tablets containing paracetamol increases by the addition of talc (0.5–1%). The stearate salts should be avoided as tablet lubricants if the active component is subject to hydroxide ion-catalyzed degradation. The degradative effect of the alkali stearates is inhibited in the presence of malic, hexamic, or maleic acid.

As a general rule, in selecting excipients, it is probably best to avoid hygroscopic excipients when formulating hydrolytically labile compounds. One of the most effective ways to stabilize a pH-sensitive drug is through adjustment of the microscopic pH of the formulation. Excipients with high pH stability and buffering agents are recommended. The equilibrium moisture content (hygroscopicity) at different relative humidities for a variety of drug and excipients would be a clue to selecting optimal formulations. If dry processing and the use of nonhygroscopic excipients still result in unacceptable rates of hydrolysis, use of a dessicant and/or moisture protective packaging can further increase stability against drug hydrolysis. The manufacturing process should be conducted under low-humidity conditions and not during the hot summer season to improve drug-exciipient compatibility.

Oxidation reactions are complex and it is difficult to understand the reaction mechanism. The best approach is to avoid excipients containing oxidative reactants such as peroxides and metal ions. The air oxidation or metal ion-catalyzed oxidation can be tested after storing the samples in the solutions. The impurities in excipients such as povidone or as degradation products in PEGs are organic peroxides and are typically more reactive than hydrogen peroxide. A commercially available organic peroxide such as *tert*-butyl hydroperoxide is better to evaluate the susceptibility of a compound to peroxide oxidation rather than the hydrogen peroxide. Reactive impurities such as peroxides and ionic chemicals (talc and titanium oxide) in the excipients commonly may act as catalysts for oxidation of the drug.

Therefore, it is essential to remove any oxidative peroxides and ionic chemicals. Use of free-radical scavengers such as butylated hydroxyanisole (BHA) or butylated hydroxytoluene (BHT) can stabilize the oxidation reaction of the drug with excipients via a free-radical mechanism. However, uniform distribution of the low levels of these antioxidants in solid formulations is quite difficult. The BHA is added to both lovastatin and simvastatin tablets. If an oxidation reaction is catalyzed by metal ions or excipients with high transition metal ion contents (talc), chelating agents can also be used to bind trace metal ions. However, citrate is often the agent of choice because of the potential toxicity of many chelating agents. Oxidation is less likely to occur if the oxidizable group of phenols/catechols and secondary and tertiary amines is protonated. If some oxidation reactions are catalyzed by light, the formulation can be stabilized by a light-absorbing coating.

Aldehyde-amine addition is also a typical reaction type. The potential aldehyde interaction also makes sense to screen out a compound as part of the preformulation evaluation. All aldoses such as lactose or excipients such as starch and microcrystalline cellulose that have terminal aldehyde groups should be avoided with the excipients having primary/secondary amines. 5-(Hydroxymethyl)-2-furaldehyde (HMF) would be a good choice since it is a degradation product of many sugars (lactose) and celluloses, at least in trace levels. The Schiff's base $[-CH=N-]$ is formed when the sugar aldehyde (lactone) and the primary/secondary amines are mixed. The isoniazide and trace level of HMF from lactose can also readily form the Schiff's base. It has been reported that the reaction of hydrazine hydrochloride and starch to form high-molecular-weight addition products gives high-molecular-weight products. The reaction of fluoxetine hydrochloride is more rapid with spray-dried lactose monohydrate.

Many excipients are acids or bases or have acidic or basic impurities. For this reason, the reaction of amines with aldehydes requires that the amine exist in the nucleophilic-free base, rather than the protonated cationic form. For example, the reaction of fluoxetine hydrochloride with lactose was much more rapid as potassium hydroxide was added to neutralize the hydrochloride salt. Michael addition between seproxetine and maleic acid from a tablet formulation following dissociation of the hydrochloride salt occurs because of the conversion of a salt to a free acid/base.

Finally, the physical instability that can occur is the cross-linking of gelatin or its capsules. Low levels of aldehyde impurities in excipients (starch, polysorbate 80, PEG, and rayon coils) and packaging materials have been reported to cause cross-linking of gelatin. Dissolution slowing is also more pronounced for wet granulation tablets than direct-compression tablets. Dissolution slowing appears to be due to hardening of the water-soluble excipients and a reduction of disintegration time.

Once suspect excipients have been eliminated from consideration, small-scale formulations with manufacturing processes such as granulation, drying, and compression can be used to assess whether interactions between excipients or processing conditions result in any unpredicted instability. The ratio of drug and excipients is also a critical factor to consider in incompatibility studies. In addition, the lower the drug dose, the greater the possibility of degradation by low-level impurities in the excipients.

In conclusion, drug-excipient compatibility studies have a key role at the early preformulation stages to select excipients or after formulation to help identify the mechanism of any detected instability [14]. An understanding of the potential physicochemical interactions of drug with known chemical reactivities of excipients and

their impurities will aid in the proper selection of excipients. Knowledge of trace impurities/additives in excipients and the consistency of these levels from batch to batch and supplies to supplier is also essential to select proper pharmaceutical excipients. Although the best solution kinetics and drug–excipient compatibility studies may be established, the possibility of unexpected instability because tablets and capsules are complex multicomponent systems must be remembered.

6.1.4 POWDER CHARACTERISTICS

Most drug and inactive excipients used in tablet formulation are in the solid state as amorphous powder or crystals of various morphological structures. There may be substantial differences in particle size, surface area, crystal morphology, wetting, and flowability as well as many physical properties of drug, excipients, and their blends [16]. Table 12 describes common micromeritic topics important to pharmaceutical preformulation.

Before their use in the solid dosage forms, it is necessary to understand and characterize the physical and chemical properties of drug, excipient, and their powder mixtures, including crystal habit, particles size, shape, flow characteristics, density, hygroscopicity, and compressibility and compaction [2, 3]. Hiestand noted that successful tableting operations require the selection of excipients that balance desirable physical, flow, and mechanical properties for tablet manufacturing [17]. The quantification of these properties using a unified approach is essential to the design and optimization of solid dosage formulations [1]. Instrumental analyses such as scanning electron microscopy (SEM), DSC, and powder X-ray diffraction (PXRD) can be very useful to characterize powder properties such as purity, polymorphism, salvation, degradation, drug–excipient compatibility, and other desirable characteristics.

6.1.4.1 Crystal Form and Habit

The morphology of a pharmaceutical solid is of importance since this property can influence the bulk powder properties. The six crystal systems are cubic, hexagonal, tetragonal, orthorhombic, monoclinic, and triclinic crystals. The observed overall

TABLE 12 Micromeritic Topics Important to Pharmaceutical Preformulation

Particle shape
Particle size distribution
Solid geometry (packing, density, porosity, void)
Surface characteristics (adsorption, area, surface energy, solubility)
Methods of determination
Chemical stability
Dynamics (flow rate, transport)
Particle separation
Processing (sieving, sedimentation, grinding, mixing, compaction)
Sampling
Drug release

shape of crystal habits comprises plate, tabular, equant, columnar, blade, and avicular as well as dendrites, treelike pattern, and spherulites, tiny crystals radiating from a center [2, 18, 19]. Crystal form (crystal habit) as well as a noncrystalline amorphous form may affect drug stability, dissolution rate, flow, mechanical properties, and ability to mix with excipients. The amorphous form of a drug has the lowest melting point and usually the fastest dissolution rate, but it is most likely to react or degrade. Mechanical properties such as flowability, miscibility, particle strength, and cohesiveness often vary among the polymorphs, crystal shapes, or habits. Cohesiveness, the surface free energy effect that results in particle aggregation, may also be different for various polymorphs and habits.

6.1.4.2 Particle Size Distribution

The determination and control of particle size distribution are often very important in pharmaceutical preformulation since the drug safety, stability, and viability of the dosage form and manufacturing process can be significantly influenced [19]. Particle shape is also important in determining particle size. The particle size of materials is readily expressed in terms of its diameter according to the definition of particle size. As the degree of asymmetry of particles increases, however, so does the difficulty of expressing size in terms of a meaningful diameter [20]. Figure 4 shows different ways of defining a diameter. The “diameter” can be simply the longest or the shortest linear dimension of the crystal. If one can calculate the area of the particle, one may obtain the diameter d_a , which is the diameter of a circle with the same area as the particle.

If all the particles in a sample are of the same size, then the powder is monodisperse. Truly, the particles have more than one size in polydisperse samples. The monodisperse particle size distribution is more desirable than the polydisperse one. Therefore, the shape and surface area of the individual particles, the size ranges based on number or weight of particles, as well as the total surface area are variable. The commonly illustrated particle forms are sphere, rod, fiber, granular, cubical, flake, condensation floc, and aggregate.

The fineness of the powder is characterized by a number (e.g., a diameter d). Particles, of course, will have different shapes so that there are different ways of defining a diameter. The technique for obtaining d_a given above has been used microscopically. More conventional is the so-called surface mean diameter, which, is the diameter of a sphere that has the same surface area as the particle. The so-called single-particle volume mean diameter is possible if there are instruments that can measure the volume of an odd-shaped particle. If the shape factor is indepen-

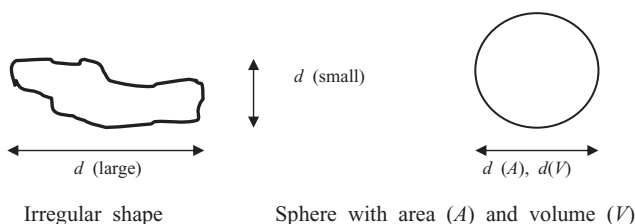


FIGURE 4 Different ways of defining a diameter.

TABLE 13 Particle Size Distribution of Powdered Cornstarch Samples

Particle Size Range (μm)	Number of Occurrences (n)	Percent Frequency	Cumulative Frequency (%)
25–27	1	8.3	8.3
27–29	3	25.0	33.3
29–31	4	33.3 (33.4)	66.7
31–33	3	25	91.7
33–35	1	8.3	100
Total	12	99.9 (100)	—

dent of the size of the particle, then the shape is called isometric. Examples of isometric shapes are cube, sphere, and cylinder.

Suppose a sample of 12 particles of corn starch with fairly narrow particle size distribution (25–35 μm) were measured. In this case, the distribution of particles is very narrow and approximately distributed as normal or Gaussian pattern. To convert these numbers into frequencies, it is noted that there are 12 particles in total; that is, dividing each number by 12 and multiplying this by 100 will give the percent frequency, as shown in Table 13.

If the frequency is plotted as a function of the midpoint of the diameter ranges, then a frequency histogram is obtained. It is noted that for the noncumulative curve the midpoints of the intervals are used, but for the cumulative curve the interval endpoint is used. When the number or weight of particles lying within a certain size range is plotted against the size range or mean particle size, a *frequency distribution curve* is obtained. However, due to the deviation from the normal distribution of particles, a lognormal distribution of the particle size is statistically plotted against the cumulative percent frequency on a probability scale, and a linear relationship is observed (Figure 5). Probability paper is a type of paper that straightens out this type of S-shaped curve. The logarithm of the particle size is equivalent to 50% on the probability scale, that is, the 50% size is known as the *geometric mean diameter* and the slope is given by the *geometric standard deviation* σ_g , which is also the quotient of the ratio: (84% undersize or 16% oversize)/(50% size) or (50% size)/(16% undersize or 84% oversize).

Many methods are available for determining particle size in pharmaceutical practice, including microscopy, sieving, sedimentation, and determination of particle volume [19]. Sieve analysis with U.S. standard sieves is widely used to determine the particle size distribution based on powder weight. Sieves are classified according to the number of openings (Table 14) and are generally made of wire cloth woven from brass, bronze, or other suitable wire.

The USP uses descriptive terms to characterize the particle size of a given powder, which are related to the proportion of powder that is capable of passing through the openings of standardized sieves of varying dimensions in a specified time period under the mechanical sieve shaker as follows:

Coarse (or a no. 20) powder: All particles pass through a no. 20 sieve and not more than 40% through a no. 60 sieve.

Moderately coarse (or a no. 40) powder: All particles pass through a no. 40 sieve and not more than 40% through a no. 60 sieve.

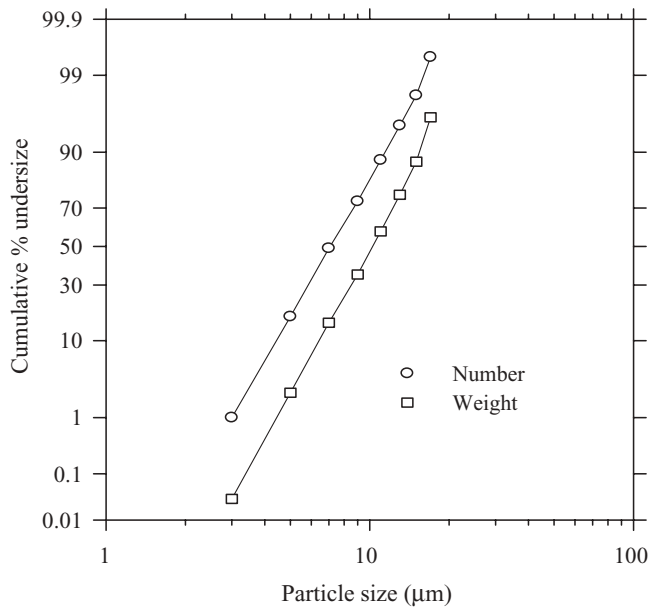


FIGURE 5 Typical lognormal distribution of particles based on weight and number.

TABLE 14 Openings of Standard Sieves

Sieve Number	Sieve Opening
2	9.5 mm
3.5	5.6 mm
4	4.75 mm
8	2.36 mm
10	2.00 mm
20	850 μm
30	600 μm
40	425 μm
50	300 μm
60	250 μm
70	212 μm
80	180 μm
100	150 μm
120	125 μm
200	75 μm
230	63 μm
270	53 μm
325	45 μm
400	38 μm

Fine (or a no. 80) powder: All particles pass through a no. 80 sieve. There is no limit as to greater fineness.

Very fine (or a no. 120) powder: All particles pass through a no. 120 sieve. There is no limit as to greater fineness.

Microscopy, in which the particles are sized through the use of a calibrated grid background or other measuring devices (range 0.2–100 μm). SEM can also readily measure the smallest particle size. The microscope allows the observer to view the actual particles, but it gives two-dimensional views. With the sedimentation rate, particle size is determined by measuring the terminal settling velocity of particles through a liquid medium in a gravitational or centrifugal environment (range 0.8–300 μm). Sedimentation rate may be calculated from the well-known Stokes equation. The sedimentation methods yield a particle size relative to the rate at which particles settle through a suspending medium, a measurement important in the development of emulsions and suspensions. With light energy diffraction (light scattering), particle size is determined by the reduction in light reaching the sensor as the particle, dispersed in a liquid or gas, passes through the sensing zone (range 0.2–500 μm). On the other hand, laser scattering utilizes a $\text{H}_3\text{-Ne}$ laser, silicon photodiode detectors, and an ultrasonic probe for particle dispersion (range 0.02–2000 μm). The measurement of particle volume using a Coulter counter allows one to calculate an equivalent volume diameter, but no information on shape of the particles is available. Laser holography, in which a pulsed laser is fired through an aerosolized particle spray and photographed in three dimensions with a holographic camera, allows the particles to be individually imaged and sized (range 1.4–100 μm). The above methods and others may be combined to provide greater assurance of size and shape parameters. Automated particle size analyzers linked with computers are commercially available for data processing, distribution analysis, and printout.

Determination and control of particle size are often prerequisites in preformulation stages because the size distribution of excipients, drug, and their mixtures can influence safety, efficacy, stability, viability of dosage form, and manufacturing processes. Furthermore, the particle size of pharmaceuticals can affect uniform mixing, flow characteristics, formulation characteristics, dose-to-dose content uniformity, dissolution rate, and bioavailability of drug. Tablet characteristics such as porosity and flowability are highly affected by the particle size as well. The smallest particles induce electrostatic forces and aggregations while the larger particles show greater weight variations. The ideal size ranges of particles are usually 10–150 μm . Therefore, detailed information of the particle size of drug, excipients, and their blends should be required in tablet formulation as well as regulatory issues. Particle size is also important in the tableting field, since it can be very important for good homogeneity in the final tablet. The particle size should be consistent throughout the production to satisfy table formulation and regulatory demands.

6.1.4.3 Flow Characteristics

Good flow properties are a prerequisite for the successful manufacture of both tablets and powder-filled hard gelatin capsules. Proper fluidity of materials is required to be transported through the hopper of a tableting machine. The elongated particle shape and small particle size could cause high tablet weight variation, strength, unacceptable blend uniformity, and difficulty in filling containers and dies. Excipients with good flow characteristics and low cohesive powders should be more preferable in tablet production. Powder flow is affected by the numerous parameters, including purity, crystallinity, electrostatic forces, mechanical

properties (brittleness, elasticity), density, size, shape, surface area, moisture content, direction and rate of shear, storage container dimension, and particle–wall interaction [19].

It is a property of all powders to resist the differential movement between particles when subjected to external stresses. A bulk powder is somewhat analogous to a non-Newtonian liquid, which exhibits plastic flow and sometimes dilatancy if the particles being influenced by attractive forces. Accordingly, powders may be free flowing or cohesive (“sticky”). The resistance to free flow is due to the cohesive forces between particles [18]. Three principal types of interparticular forces are forces due to electrostatic charging, van der Waals forces, and forces due to moisture. Electrostatic forces are dependent on the nature of the particles, in particular their conductivity. Van der Waals forces are the most important forces for most pharmaceutical powders. These forces are inversely proportional to the square of the distance between the two particles and hence diminish rapidly as particle size and separation increase. Powders with particles below $50\mu\text{m}$ will generally exhibit irregular or no flow due to van der Waals forces. Particle shape is also important; for example, the force between a sphere and a plane surface is about twice that between two equal-sized spheres. At low relative humidity, moisture produces a layer of adsorbed vapor on the surface of particles. Above a critical humidity, typically in the range 65–80%, it will form water liquid bridges between particles. Where a liquid bridge forms, it will give rise to an attractive force between the particles due to surface tension or capillary forces. The role of the formulator is to ensure that the flow properties of the powder are sufficient to enable its use on modern pharmaceutical equipment, powder hoppers, and flow through orifices in the tablet production.

It is important that the powder flows from the hopper to the filling station of the tablet machine at an appropriate rate and without segregation occurring. There are two types of flow that can occur from a powder hopper: *core flow* and *mass flow* [2]. Figure 6 shows the two different powder flow patterns in hoppers. When a small amount of powder is allowed to leave the hopper, there is a defined region in which downward movement takes place and the top surface begins to fall in the center. A core flow hopper is characterized by the existence of dead spaces during discharge. A mass flow hopper is one in which all the material is in motion during discharge, in particular the areas adjacent to the hopper wall. As a small amount of powder is discharged, the whole bulk of the powder will move downward. Whether core flow or mass flow is achieved is dependent on the design of the hopper (geometry and wall material) and the flow properties of the powder.

Powder flow into orifices is also important when filling dies in tablet machines and in certain types of capsule-filling machines. For a given material, the flow into or through an orifice is dependent on the particle size (Figure 7). In general, as the particle size increases, the powder flow rate also increases. However, there is practically no flow if the particle size is below $50\mu\text{m}$ or above $1200\mu\text{m}$. The Carr index gives us the guidance for powder flowability. A lower Carr index of excipients is more desirable for acceptable powder flow. At the lower end of the particle size range, cohesive forces will result in poor flow. Powders with particles below $50\mu\text{m}$ will generally exhibit irregular or no flow due to van der Waals forces. As the particle size increases, the flow rate increases until a maximum is achieved, at an orifice diameter–particle diameter ratio of 20–30. As the particle size continues to increase,

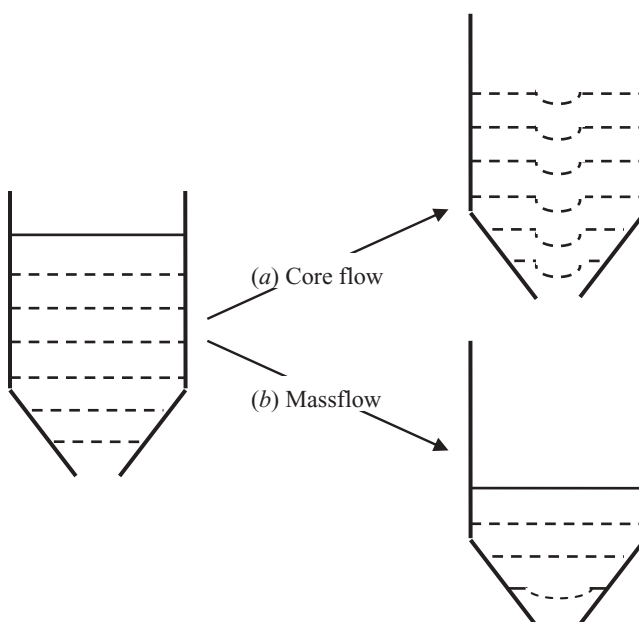


FIGURE 6 Powder flow patterns in hoppers.

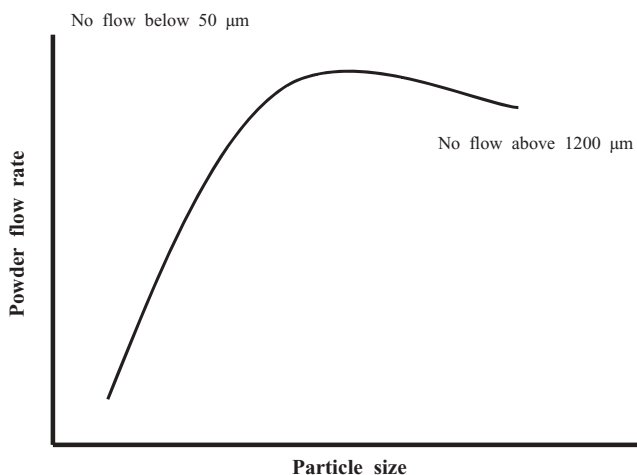


FIGURE 7 Effect of particle size on rate of powder flow through orifice.

the rate decreases due to mechanical blocking or obstruction of the orifice. Flow will stop completely when the orifice-particle ratio falls below 6 and if the size is above 1200 μm .

There are several different methods available for determining the flow properties of powders. *Shear cell methods* provide an assessment of powder flow properties as a function of consolidation load and time. There are a number of types of shear cells available, the most common being the Jenike shear cell [21].

Common indices of flowability are the *Hausner ratio* and the *Carr index* (compressibility). The increase in bulk density of a powder is related to the cohesiveness of a powder. So measurement of the bulk density of a powder is essential to define the flow characteristics. Ratios of poured-to-tapped bulk densities are expressed in two ways to give indices of flowability:

$$\text{Hausner ratio} = \frac{\text{tapped bulk density}}{\text{poured bulk density}}$$

$$\text{Carr index (compressibility)} = \frac{100 \times (\text{tapped bulk density} - \text{poured bulk density})}{\text{poured bulk density}}$$

The Hausner ratio varies from about 1.2 for a free-flowing powder to 1.6 for cohesive powders. Carr index classifications for flowability [2] are listed in Table 15.

Compressibility indices are a measure of the tendency for arch formation and the ease with which the arches will fail and, as such, is a useful measure of flow. A limitation of the bulk density indices for flow characteristics is that they only measure the degree of consolidation; they do not describe how rapidly consolidation occurs. *Angle of repose* is a common method used to measure powder flow with small sample quantity. If powder is poured from a funnel onto a horizontal surface, it will form a cone due to gravitational forces. The angle between the sides of the cone and the horizontal is referred to as the angle of repose. So there is a correlation between powder flow and angle of repose. The relationship between the Carr index and angle of repose is now discussed. The angle of repose is a measure of the cohesiveness of the powder, as it represents the point at which the interparticle attraction exceeds the gravitational pull on a particle. A free-flowing powder will form a cone with shallow sides, and hence a low angle of repose, while a cohesive powder will form a cone with steeper sides. As a rough guide, angles less than 30° are usually indicative of good flow, while powders with angles greater than 40° are likely to be problematic.

The *avalanching behavior* of powder is also a measure of flowability. If a powder is rotated in a vertical disc, the cohesion between the particles and the adhesion of the powder to the surface of the disc will lead to the powder following the direction of rotation until it reaches an unstable situation where an avalanche will occur. After the avalanche, the powder will again follow the disc prior to a further avalanche.

TABLE 15 Carr Index Classification and Powder Flowability

Carr Index (%)	Flow
5–12	Free flowing
12–16	Good
18–21	Fair
23–35	Poor
33–38	Very poor
>40	Extremely poor

Measurement of the time between avalanches and the variability in time is a measure of the flow properties of the powder.

If a powder flows poorly, the vibrator can be used, but it also causes powder segregation and stratification. The addition of glidant (occasionally lubricant) in the powder mixtures can readily increase flowability at the low concentration. Talc or fumed silicon dioxide is an example of a glidant. If this is not sufficient to improve the flow, other means of flow improvement are necessary. There are two main factors that affect powder flow: particle size and particle shape. The more spherical a particle is, the better it flows. Small particles are very cohesive and hence do not flow well, but increasing the particle size will improve flow. With the aid of spray drying or spheronizers, particles become spherical.

In general, powder below 50 μm is not very free flowing because the cohesive forces below this size become stronger than the gravitational force, and flow through the orifice is prevented. This, of course, is a function of the size of the orifice, and flow might be possible in a larger orifice.

Particle size enlargement of the drug substance can be brought about by manipulation of the recrystallization step in the synthesis of the drug. To increase powder flow, particle size enlargement by slugging, roller compaction, and wet granulation can be used. If a powder is compressible but does not flow well, then slugging may be employed. In slugging, tablets are made of the poorly flowing substance on a high-duty, slowly operating machine into large dies. The dies are large so that the flow is sufficiently increased, but now the compression forces must be increased because the larger area dictates a larger force to attain a given pressure (the elastic limit being in stress units). In roller compacting, the powder is processed between two heavy-duty rollers, compacted between the rolls, and emerges as a compressed sheet, which is then milled. These two methods are necessary if the drug substance (e.g., aspirin) is sufficiently moisture sensitive and there are stability issues so it cannot be wet granulated. Otherwise, wet granulation is a frequently used method of particle enlargement for free-flowing powder.

6.1.4.4 Density and Bulkiness

Density When a powder is poured into a container, the volume that it occupies depends on a number of factors, such as particle size, particle shape, and surface properties. In normal circumstances, it will consist of solid particles and interparticulate air spaces (voids or pores). The particles themselves may also contain enclosed or intraparticulate pores. If the powder bed is subjected to vibration or pressure, the particles will move relative to one another to improve their packing arrangement. Ultimately, a condition is reached where further densification is not possible without particle deformation. The density of a powder is therefore dependent on the handling conditions to which it has been subjected, and there are several definitions that can be applied either to the powder as a whole or to individual particles.

Because particles may be hard and smooth in one case and rough and spongy in another, one must express densities with great care. Density is universally defined as weight per unit volume. Three types of densities—true density, particle density, and bulk density—can be defined, depending on the volume of particles containing microscopic cracks, internal pores, and capillary spaces.

The true density is the material itself exclusive of the voids and interparticulate pores larger than molecular or atomic dimension in the crystal lattice. Particle (granular) density, determined by the displacement of mercury, which does not penetrate at ordinary pressure into pores smaller than $10\mu\text{m}$, is the mass of the particle divided by its volume. The different terms arise from the definition of volume: *True particle density* is when the volume measured excludes both open and closed pores and is a fundamental property of a material; *apparent particle density* is when the volume measured includes intraparticulate pores; *effective particle density* is the volume “seen” by a fluid moving past the particles. *Bulk density* (powder density) is the volume in a graduated cylinder including both the particulate volume and the pore volume. The bulk density will vary depending on the packing of the powder. Based on the definition of volume, *minimum bulk density* is when the volume of the powder is at a maximum, caused by aeration, just prior to complete breakup of the bulk. *Poured bulk density* is when the volume is measured after pouring powder into a cylinder, creating a relatively loose structure. *Tapped bulk density* is, in theory, the maximum bulk density that can be achieved without deformation of the particles.

Based on the definition of density, two new terms are defined. *Porosity* is defined as the proportion of a powder bed or compact that is occupied by pores and is a measure of the packing efficiency of a powder and *relative density* is the ratio of the measured bulk density and the true density:

$$\text{Porosity} = 1 - \frac{\text{bulk density}}{\text{true density}}$$

$$\text{Relative density} = \frac{\text{bulk density}}{\text{true density}}$$

Bulkiness The specific bulk volume, the reciprocal of bulk density, is often called *bulkiness* or *bulk*. It is an important consideration in the packaging and filling of powders for tablet production. The bulk density of calcium carbonate can vary from 0.1 to 1.3, and the lightest or bulkiest type would require a container about 13 times larger than the heaviest type. Bulkiness increases with a decrease in particle size. In a mixture of materials of different sizes, however, the smaller particles sift between the larger ones and tend to reduce the bulkiness.

To define bulkiness in detail, the porosity and density of powders should be understood. Suppose a powder, such as zinc oxide, is placed in a graduated cylinder and the total volume is noted. The volume occupied is known as the bulk volume V_b . If the powder is nonporous, that is, has no internal pores or capillary spaces, the bulk volume of the powder consists of the true volume of the solid particles plus the volume of the spaces between the particles. The volume of the spaces, known as the void volume v , is given by equation

$$v = V_b - V_p$$

where V_p is the *true volume* of the particles.

The *porosity* or *voids* (ϵ) of a powder is also defined as the ratio of the void volume to the bulk volume of the packing given below. Porosity is frequently expressed in percent, $\epsilon \times 100$:

$$\epsilon = \frac{V_b - V_p}{V_b} = 1 - \frac{V_p}{V_b}$$

6.1.4.5 Hygroscopicity

The hygroscopicity of a drug and pharmaceutical substances is a potential parameter to be considered in tablet formulation. The moisture uptake rate is quite variable depending on the type of drug and excipients as well as the environmental conditions. So, a concise definition of hygroscopicity is not possible. Powders can absorb moisture by both capillary imbibition and swelling. The instantaneous water absorption properties of pharmaceutical excipients correlate with total surface area while the total absorption capacity correlates with powder porosity [22].

If drug and excipients are so hygroscopic, they can readily adsorb water until they deliquesce, or begin to dissolve. Moisture adsorption is important because adsorbed water can cause incorrect weighing and degradation of drug and/or excipients. The drug, excipients, and water reaction will continue as the amount of water increases. When a solid is placed in a room, moisture will condense onto it. If this occurs simply as a limited amount of adsorbed moisture, then the substance is not hygroscopic under these conditions. These conditions exist if the water vapor pressure in the surrounding atmosphere is lower than the water vapor pressure over a saturated solution of the solid in question. However, if the water vapor pressure in the atmosphere is higher than that of the saturated solution, there will be a thermodynamic tendency for water to condense upon the solid materials (drug and excipients).

The drug and pharmaceutical excipients adsorb or lose the moisture depending on the relative humidity in the atmosphere. The nonhygroscopic materials are not affected by the moisture and are in an equilibrium state. In general, solid dosage forms such as tablets or capsules should be hydrophilic because the solid materials must dissolve after swallowing. However, solid dosage forms must also be stable against physical and chemical factors.

The moisture uptake rates (MUR) can simply be obtained by weighing the sample after a given time (six days), but in such a case it is assumed that the moisture uptake is still in the linear phase. If, for instance, the weight gain is 5 mg per 10-g sample in six days, then the MUR is $5/(10 \times 6) = 0.083 \text{ mg/g/day}$. If the MUR values are plotted versus relative humidity (RH) and the curve that intercepts the x axis at 20% RH is obtained from a straight line, the compound can be stored without moisture pickup in atmospheres of less than 20% RH. In addition, the hygroscopicity of materials is indicated as follows:

$$\text{Loss of drying (LOD \%)} = \frac{\text{weight of water in sample}}{\text{total weight of wet sample}} \times 100$$

$$\text{Moisture content (MC \%)} = \frac{\text{weight of water in sample}}{\text{weight of dry sample}} \times 100$$

$$\text{Equilibrium moisture contents (EMC)} = \frac{\% \text{ LOD}}{\% \text{ LOD} + 100} \times 100$$

$$\text{Relative humidity (RH)} = \frac{\text{water vapor pressure in atmosphere}}{\text{saturated water vapor pressure}} \times 100$$

Depending on the hygroscopicity based on the EMC, various drug and excipients are classified in four groups (Table 16).

Figure 8 also shows an example of moisture uptake for four selected excipients as a function of relative humidity. Depending on the hygroscopicity of the excipients, the uptake behaviors are quite variable. Excipients such as microcrystalline cellulose (MCC) and starch can pick up significant amounts of water at relatively low relative humidity. Since this water is not present as a hydrate, it is potentially free to interact with a drug.

TABLE 16 Classification of Hygroscopicity and Example Pharmaceutical Excipients

Type I: Nonhygroscopic	Type II: Slightly Hygroscopic	Type II: Moderately Hygroscopic	Type IV: Very Hygroscopic
No MC change below RH 90% or less than 20% MC changes at RH 90% after 1 week storage	No MC change below RH 80% or less than 40% MC changes at RH 80% after 1 week storage	Not more than 5% MC change below RH 60% or less than 50% MC changes at RH 70% after 1 week storage	Increase of MC at RH 40–50% or more than 70% MC changes above RH 40% after 1 week storage
<i>Examples</i>			
Lactose USP	MCC	HPC	Povidone
Dicalcium phosphate	Sucrose, dextrose	HPMC	Sodium starch glycolate
Ethylcellulose	Poloxamer 188	Bentonite	Polyplasdone XL
Magnesium stearate	PEG 3350	Pregelatinized starch	Sorbitol
	CAP	Starch USP, Corn	CMC Na
		Gelatin USP	

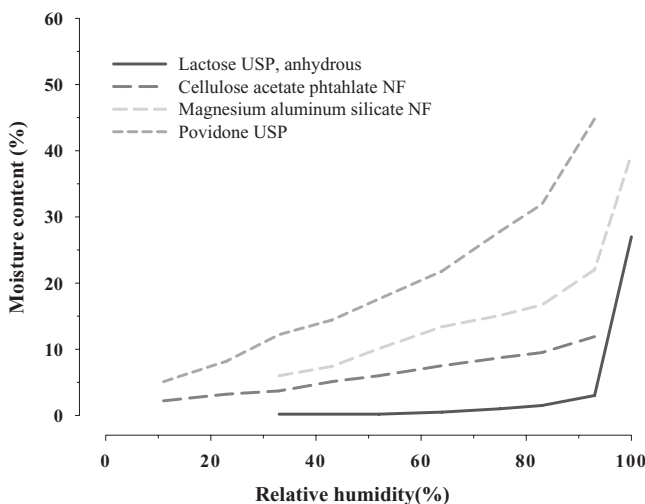


FIGURE 8 Profiles of moisture uptake for four selected excipients as function of relative humidity.

The moisture content of drug can affect the cohesiveness of particles through hydrogen bonding or by changing surface energy effects. Water also can act as a plasticizing agent and can lower the glass transition temperature of amorphous polymorphs, thus allowing a rubbery state to exist at a lower temperature. Water also can take up intra- and intergranular pore spaces (capillaries) of powders by acting as an interparticle bridge through surface adsorption mechanisms.

The hygroscopicity of materials influences the flowing characteristics of drug and excipients by forming adsorption film with an aid of water as a solvent. Dissolution of drug and excipients from solid dosage forms can also occur. The crystallinity of troglitazone-PVP K30 solid dispersions can be changed by the water content [23]. During manufacturing operations, water's ability to act as a bridge between particles can improve the compression capabilities of powder masses and affect the tensile strength and hardness of the tablet. The milling or blending is also changed. Most of all, the chemical hydrolysis of labile materials is more facilitated, resulting in low stability during storage. Adsorbed water also can act locally as a solvent, and in many cases drug–excipient incompatibility occurs by dissolving drug or excipients in granulation or blended powder mass, as observed when aspirin tablets liberate a strong odor of free salicylic acid. Any free, unbound water in the mass can migrate throughout the material mass and act as a reagent. A waterproof packaging or container is used for many moisture-sensitive materials.

6.1.4.6 Mixing

The mixing of powders is a key step in the manufacture of virtually all solid dosage forms. In general, particle size, shape, and surface energy are important factors for blending of drug and excipients in unit operations. The perfect mixing of powder is desirable, that is, a mixture in which the probability of finding a particle of a given component is the same at all positions in the mixture, but the powder mixing has a maximum degree of randomness (Figure 9). To determine the degree of mixing obtained in a pharmaceutical operation, it is necessary to reasonably sample the mixture and determine the variation within the mix statistically [2].

Uniform mixing of powdered materials occurs if they have similar particle size distributions and particle shapes. Spherical particles mix least well while plate and fiber shapes also do not mix well because they tend to clump. The more cohesive the material, the more difficult it is to mix that material with other materials. Similarly, cohesiveness between drug and excipient or among excipients may hinder the

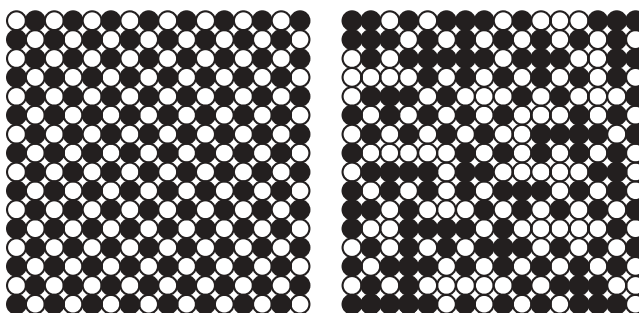


FIGURE 9 Comparison of powder mixing: perfect mixing and random mixing.

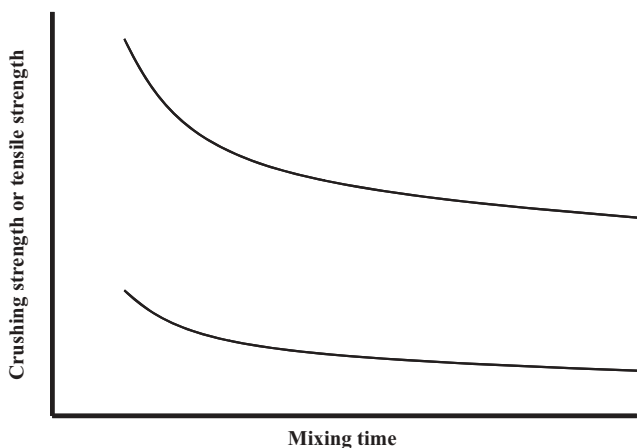


FIGURE 10 Effect of mixing time on mechanical strength of excipients.

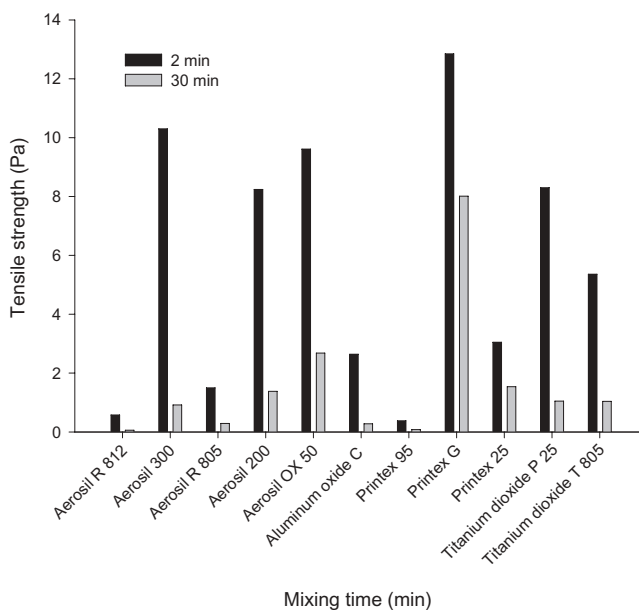


FIGURE 11 Effect of mixing time on tensile strength.

successful blending process. Ideally, the uniform mixing of powders should be such that the weight of sample taken is similar to the weight that the powder mix contributes to the final dosage form.

Figure 10 shows the effect of mixing time on the mechanical strength of powders. As the mixing time increases, the tensile strength of powders (or crushing strength of the tablet) gradually decreases [24, 25]. While the strength decreases with increasing mixing time for all materials tested, the effect is far more marked for materials that deform plastically. For example, the glidant tensile strength invariably decreases as the mixing time (2 min vs. 3 min) increases (Figure 11). There is no direct correlation of tensile strength with primary particle size of glidant (Figure 12). However,

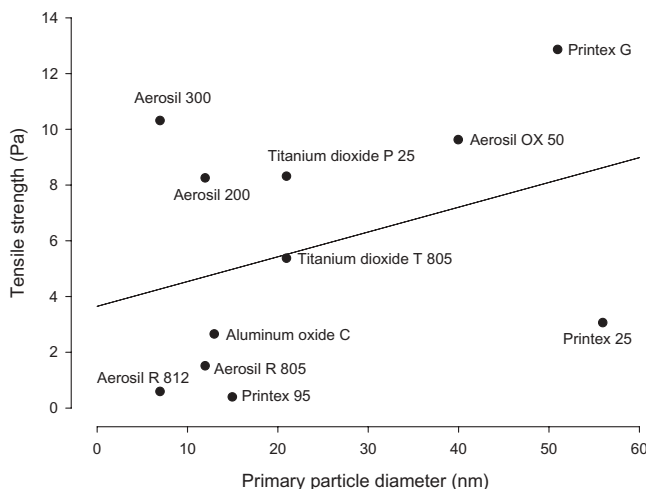


FIGURE 12 Correlation of tensile strength with primary particle size of glidant.

this correlation was further improved when some outlying glidant (Aerosil 200 and 300 and Printex 25) were excluded (R^2 values of 0.1287–0.8616).

If a powder consisting of two materials both having identical physical properties is mixed for a sufficient time, random mixing will eventually be achieved. Unfortunately, most pharmaceutical powders consist of mixtures of materials with differing physical properties, such as size, shape, density, and surface area, leading to segregation among particles, where particles of similar properties tend to collect together in part of the powder. When segregating powders are mixed, as the mixing time is extended, the powders appear to unmix. The differences in particle size are the most important for segregation in pharmaceutical powders. One exception to overcome segregation is ordered mixing rather than random mixing. When one component of a powder mix has a very small particle size (less than $5\text{ }\mu\text{m}$) and the other is relatively large, the fine powder may coat the surface of the larger particles, and the adhesive forces will prevent segregation, known as ordered mixing. This ordered mixing makes the powders produce greater homogeneity than by random mixing. The percolation of fine particles is also a factor. If the particles sizes are quite different, the smaller particles can drop easily and move to the bottom of powder, resulting in segregation. This segregation process can occur whenever movement of particles by vibration, shaking, and pouring takes place.

6.1.4.7 Particle Size Reduction (Micronization and Milling)

Mechanical attrition, that is, high-energy ball milling of powders, is a nonequilibrium processing method that has generated the reduced particle size and the formation of physically metastable materials. It can be used to modify materials by refining the microstructure, homogenizing the composition, extending solid solubility, creating metastable crystalline phases, or producing metallic glass. High-energy ball milling is both a processing method to reduce particle size and a route to the physical synthesis of metastable materials. Early in product development, when only small amounts of drug are available, comminution (grinding/mixing) may be carried out with a mortar and pestle. For larger batches, ball milling or micronization can be

used to reduce the particle size because comminution or grinding are not practical due to the length of time required [18].

There are numerous methods of particle size reduction, but their application is dependent on the intended particle size, particle distribution, cleaning convenience, operating cost, dust containment, temperature, and flexibility. The type of milling machine includes slurry, fluid energy (jet), universal, cone, and hammer. This size reduction process may reduce the risk of dissolution rate-limited bioavailability of drugs. Particle size reduction can be accomplished by using a hammer mill or a similar mill, but this process may only break up the larger crystal aggregates without significantly changing the distribution of smaller particle sizes. On the other hand, air jet mills, which impinge two streams of particles at a right angle to each other in high-velocity air streams, reduce particle size significantly within micro-sized ranges.

Ball milling was the most commonly used at the preformulation stage to reduce the particle size of small amounts of a compound. Ball mills reduce the size of particles through a combined process of impact and attrition. Usually they consist of a hollow cylinder that contains balls of various sizes which is rotated to initiate the grinding process. Micronized particles are typically less than 10 μm in diameter. The efficiency of the milling process is affected by rotation speed, number of balls, mill size, wet or dry milling, amount of powder, and length of time of milling. Although ball milling can effectively reduce the particle size of compounds, prolonged milling may be detrimental in terms of changes of compound crystal form from crystalline to polymorphic or amorphous form and stability.

Although ball milling on a large scale is possible, hammer milling is more preferable in the pharmaceutical industry. Powder is fed into the mill house via the hopper, and the rotating hammers impact with the powder. When this is fine enough to pass the screen, the powder will exit. The powder exiting will have a maximum particle size of that of the screen. The average particle size of the milled powder will be smaller, the smaller the feed rate, the more rapid the milling speed (rpm's), and the finer the screen. The knife has a blunt edge on one side and a knife edge on the other. Milling with the blunt edge forward gives rise to a smaller average particle size. The usual minimum particle range is about 50 μm . Large, heavy-duty hammer mills (micropulverizers) give much smaller particle size further down, typically to 20 μm . If particle sizes less than 5 μm are desired, micronizers are used.

If particle sizes in the micrometer range are required, then the attrition mill can be used. Here particles are fed into a chamber in which great turbulence has been created by two inlets of air at different pressure. The particles hit one another and are removed by centrifugal means and collected in a cyclone setup or in a bag above the cyclone. Such particles become highly electrically charged during the operation and also become very cohesive.

The milling process provides energy to the powders so that melting occurs if their melting point is sufficiently low. There is no guarantee that the original polymorph and habit will be regained upon resolidification. The milling and micronization process can also reduce the particle size of poorly soluble drugs so that the maximum surface area is exposed to enhance the solubility and dissolution properties. Although micronization of the drug offers the advantage of a small particle size and a larger surface area, it can also result in processing problems due to high dust, low density,

and poor flow properties. Indeed, micronization may be counterproductive, since the micronized particles may aggregate, which may decrease the surface area. Milling and micronization process also induce the changes of crystallinity of drug into amorphous form. It has been shown that the amorphous change of the crystalline structure can be achieved by vapor condensation, supercooling of melt, rapid precipitation from solution, and mechanical applications of a crystalline mass by milling or compaction [26].

Particle size reduction of the powder has produced defects on the surface that, if enough energy is imparted, leads to amorphous regions on the surface. In turn, these regions are found to have a greater propensity to adsorb water. The dissolution rate increases as the particle size of drug powder decreases due to its greater surface area for wetting.

It is known that ball milling and other types of milling can change the morphology of a solid, for example, make a crystalline compound amorphous, increase the surface energy of a solid, and distort the crystal lattice. For example, the crystalline solid state of sorbitol exhibits a complex polymorphism made of five different forms called A-, B-, Γ -, Δ -, and E-sorbitol [27]. The structures of these polymorphs have been identified by single-crystal X-ray diffraction. The structure of the Γ form is also the most stable and the most common polymorph of sorbitol. It was reported that the Γ form of sorbitol underwent a complete transformation toward the A form upon ball milling and also was affected by milling time. The DSC and XRPD patterns are useful in identifying these phenomena, although the low level of amorphous character cannot be detected by techniques such as XRPD and DSC. Crystal structures by the milling process as well as compaction forces have been shown [2].

6.1.4.8 Compaction(Compressibility)

Compressibility is the property of forming a stable and intact mass when pressure is applied. The manufacture of tablets involves the process of powder compaction or compressibility, the purpose of which is to convert a loose incoherent mass of powder into a single solid object. A protocol to examine the compression properties of flowing powder should be considered by the formulation scientist when selecting the excipient, the formulation type, and the manufacturing process, for example, direct compression or granulation for the intended solid dosage form. Acetaminophen is poorly compressible whereas lactose compresses well. In general, drug and excipients, including lubricant, are blended in a tumbler mixer for a period of time and then compressed into tablets in a hydraulic press. The crushing strength is also determined to test the compressibility of tablet at room temperature.

The compression of drug powder may change the crystal structure into a polymorphic form—likewise in the milling process. The PXRD patterns and DSC of a drug can detect these phenomena. Knowledge of the crystal structure of a drug is a prerequisite for compaction.

To fully understand the compaction behavior of a material, it is necessary to be able to quantify of its elasticity, plasticity, and brittleness. A powder in a container subjected to compressive force will undergo particle rearrangement [28]. The density of the bed will increase with increasing pressure at a characteristic rate. Brittle materials will undergo fragmentation, and the fine particles formed will percolate through the bed to give secondary packing. Plastically deforming materials will

distort to fill voids and may also exhibit void filling by percolation. When the limit of plastic deformation is reached, fracture occurs.

Many of the basic principles of compaction and the test methodologies are currently employed in pharmaceutical formulation. To characterize the compaction properties of a material or formulation, it must be possible to measure the relationship between the force applied to a powder bed and the volume of the powder bed. There are two principal types of compaction studies used to characterize materials: pressure–volume relationships and pressure–strength relationships. While ultimately it is the strength of a tablet that is important, the pressure–volume relationships provide information about the compaction properties of a material that allows an appropriate formulation to be developed. The instrumented tableting machine provides information for compaction that is directly relevant to production conditions. The compression profiles differ from those of rotary tableting machines used for commercial production. The profile of a single punch involves the powder bed being compressed between a moving upper punch and a stationary lower punch, while on a rotary machine, both punches move together simultaneously. A major advantage of instrumented machines is that they provide information not only on the compaction properties but also on flow and lubrication. The disadvantage of using instrumented rotary machines is the large quantity of materials required.

A large number of equations have been proposed to describe the relationship between pressure and volume reduction during the compaction process. The most widely used equation to describe the compaction of powders is the Heckel equation. Pharmaceutical powders do not produce perfect straight lines, and the type of deviation provides information about the compaction behavior of the material. A typical Heckel plot for a pharmaceutical powder is obtained showing a straight-line portion over a certain pressure range with a negative deviation at low pressures and a positive deviation at high pressures. The strength of tablets has traditionally been determined in terms of the force required to fracture a specimen across its diameter. The fracture load obtained is usually reported as a hardness value. Initially, most materials will demonstrate an increase in tensile strength proportional to the compaction pressure applied. As the compaction pressure increases, the tablet approaches zero porosity, and large increases in pressure are required to achieve small volume reductions [28]. Some materials will attain a maximum strength, and subsequent increases in pressure will produce weaker tablets. Other materials will also display an initial increase in strength proportional to the applied pressure, but the strength reaches a maximum before falling off sharply, resulting in capping or lamination in tablet production [28]. Figure 13 shows the correlation of hardness with compression pressure. Capping is the partial or complete removal of the crown of a tablet from the main body, while lamination is the separation of a tablet into two or more distinct layers. If the compressibility and flow of powders are good, it is possible to directly compress the powders into tablet. If either compressibility or flow is not satisfactory, roller compact, slugging, or wet granulation can be utilized to improve compressibility.

6.1.4.9 Surface Area and Other Properties

The surface area of particles is related to particles size, as discussed previously. The surface area of powders affects the drug dissolution rate, powder flow, cohesiveness, and adsorption. Furthermore, the surface area of solid materials may also

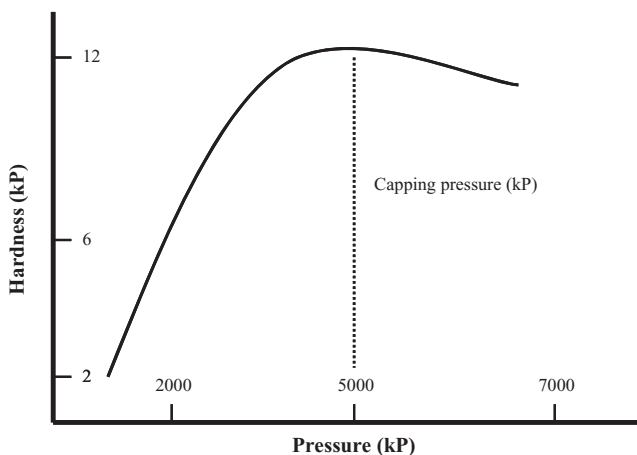


FIGURE 13 Correlation of compression pressure with hardness.

influence the physicochemical properties, adsorption, dissolution, and bioavailability of drugs.

The particle size and surface area distributions of pharmaceutical powders can be obtained by microcomputerized mercury porosimetry. Mercury porosimetry gives the volume of the pores of a powder, which is penetrated by mercury at each successive pressure; the pore volume is converted into a pore size distribution. Two other methods, adsorption and air permeability, are also available that permit direct calculation of surface area. In the adsorption method, the amount of a gas or liquid solute that is *adsorbed* onto the sample of powder to form a monolayer is a direct function of the surface area of the sample. The air permeability method depends on the fact that the rate at which a gas or liquid permeates a bed of powder is related, among other factors, to the surface area exposed to the permeant. The determination of surface area is well described by the BET (Brunauer, Emmett, and Teller) equation.

The wetting behavior of powders is an also important factor for drug dissolution. If the wetting is not satisfactory, hydrophilic excipients (lactose) and surfactant (sodium lauryl sulfate or polysorbate) are combined in the powder mixtures. The contact angle is used as an index of wetting. The lower the contact angle, the better the wetting occurs.

The general appearance of a tablet with good visual identity and overall “elegance” are essential for consumer acceptance, quality control of lot-to-lot uniformity, general tablet-to-tablet uniformity, and monitoring trouble-free manufacturing. Control of the general appearance of a tablet involves the measurement of a number of attributes, such as a tablet’s size, shape, color, presence or absence of and odor, taste, surface texture, physical flaws and consistency, and legibility of any identifying markings.

6.1.5 TABLET CHARACTERIZATION

In order to formulate the optimal tablet, various properties should be considered, including drug–excipient compatibility, flowability, lubricity, appearance, dissolution, and disintegration [2]. The prepared tablet must also meet physical specification and

quality standards according to the monograph of the pharmacopeia. In general, weight and its variation, content uniformity, thickness, hardness, friability disintegration, and dissolution should be considered for tablet validation [3]. These factors must be controlled during tablet production (in-process control) and are validated after the production to ensure the quality standards.

6.1.5.1 Disintegration

Immediate-release tablets should be readily disintegrated in the stomach when swallowed. This disintegration involves bursting apart the compact masses by aqueous fluid penetrating the fine pore structure of tablet. Disintegration testing is an important part of in-process control testing during production to ensure batch-to-batch uniformity, but its role in end-product testing has largely been superseded by dissolution testing because recently modified-release preparations are getting popular. It was recognized in the 1940s that tablets had to disintegrate in order for them to be bioavailable due to lack of biopharmaceutical information and primarily analytical limitations. Later, of course, in the 1950s and 1960s, the pharmaceutical scientist became aware of the importance of dissolution rates as well.

In general, for the medicinal agent in a tablet to become fully available for absorption, the tablet must first disintegrate and discharge the drug to body fluids for dissolution. The general manner in which a tablet disintegrates is as follows: (a) the tablet wets down, (b) the dissolution liquid penetrates the pore space, (c) the disintegrant absorbs water and swells, and (d) this swelling causes the tablet to break down into granules. Figure 14 shows the disintegration pathways of solid dosage forms for the dissolution and absorption of drugs. After the disintegration process, the solid dosage forms change into granules or smaller and fine particles ready for dissolution and absorption in the fluid.

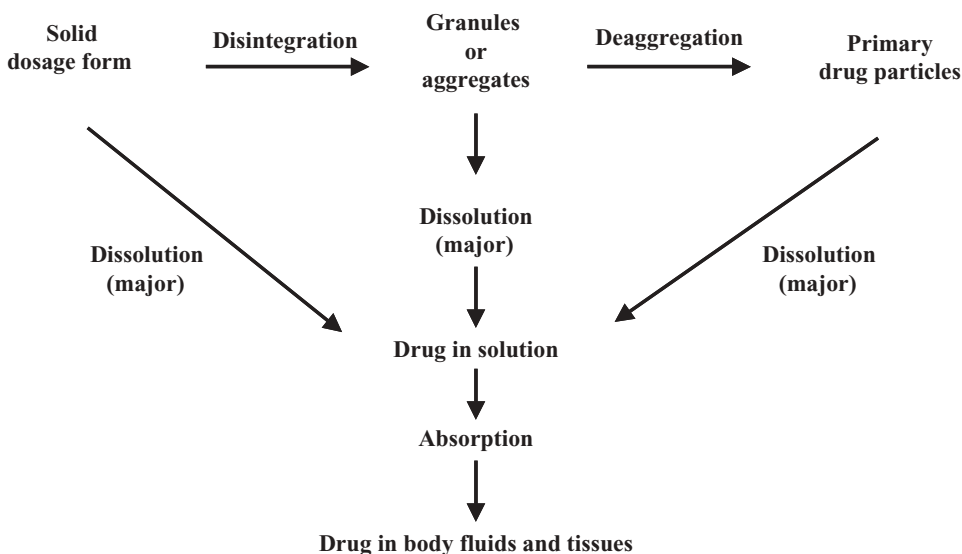


FIGURE 14 Disintegration and dissolution pathways of solid dosage forms for absorption of drug.

Tablet disintegration is the important first step in the dissolution of the drug substance contained in immediate-release tablets but dissolution is more meaningful in case of many modified release products rather than disintegration. A number of formulation and manufacturing factors can affect the disintegration and dissolution of a tablet, including the particle size of the drug substance in the formulation; the solubility and hygroscopicity of the formulation; the type and concentration of the disintegrant, binder, and lubricant used; the manufacturing method, particularly the compactness of the granulation and the compression force used in tableting; and the in-process variables which may occur. Therefore, it is vitally important for batch-to-batch consistency to establish disintegration and dissolution standards and controls for both materials and processes.

Tablet disintegration also is important for those tablets containing medicinal agents (such as antacids and antidiarrheals) that are not intended to be absorbed but rather to act locally within the GI tract. In these instances, tablet disintegration provides drug particles with an increased surface area for localized activity within the GI tract.

It is evident that there are some correlations of physical parameters with tablet disintegration time. Figure 15 shows the correlation of water penetration force, disintegration force, disintegrant contents, and compression forces of the tablet with disintegration time of the tablet. As the water penetration force increases, the tablet disintegration force also increases, resulting in shorter disintegration time [29, 30]. The amount of disintegrant in the tablet also decreases the disintegration time. The disintegration time increases as tableting pressure increases below the critical capping pressure [18]. At very low pressures the penetration of liquid into the tablet is virtually unhindered (almost like pouring water into a breaker) but the pores will be too large to allow disintegrant swelling to cause stress and the disintegration time will decrease. Once the pores are sufficiently small, penetration of the liquid into the disintegrant becomes the limiting step, and the disintegration time will increase

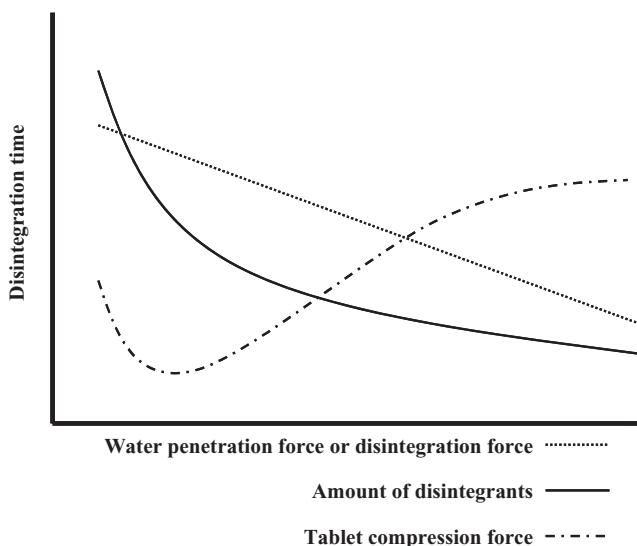


FIGURE 15 Correlation of physical parameters on tablet disintegration time.

with increasing pressure. Disintegrants and lubricants are added to wet-granulated products after the granulation has been dried. Disintegration time increases as the amount of hydrophobic lubricant increases. The mixing time for the lubricant must be kept short because otherwise the lubricant may fluidize during the mixing step and lose part of the lubricant properties that are necessary for flow in the tablet die. If the disintegration is not satisfactory, numerous types of disintegrants are added in the tablet formulations, including starch, croscarmellose sodium, sodium starch glycolate and crospovidone known as superdisintegrants. In general, the swelling rate and water uptake are the most important properties of disintegrants.

All USP tablets must pass a test for disintegration, which is conducted in vitro using a testing apparatus. The detailed monograph for disintegration testing is described in the many pharmacopeias [2, 3].

The apparatus consists of a basket-rack assembly containing dimensions held vertically upon a 10-mesh stainless steel wire screen. During testing, a tablet is placed in each of the six tubes of the basket, and the mechanical device raises and lowers the basket in the immersion fluid at a frequency of between 29 and 32 cycles per minute, the wire screen always maintained below the level of the fluid. For uncoated tablets, buccal tablets, and sublingual tablets, water maintained at about 37°C is used as the immersion fluid unless another fluid is specified in the individual monograph. For these tests, complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core. Buccal tablets must disintegrate within the time set forth in the individual monograph, usually 30 min, but varying from about 2 min for nitroglycerin tablets to up to 4 h. If one or more tablets fail to disintegrate, additional tests prescribed by the USP must be performed. Enteric-coated tablets are also similarly tested, except that the tablets are permitted to be tested in simulated gastric fluid for 1 h with no sign of disintegration, cracking, or softening. They are then switched to the simulated intestinal fluid for the time stated in the individual monograph during which time the tablets disintegrate completely. If 1 or 2 of the 6 tablets fails to disintegrate completely, disintegration testing is repeated on 12 additional tablets, and not less than 16 of the total 18 tablets tested must disintegrate to meet the standards.

6.1.5.2 Dissolution

Definitions Dissolution is the dynamic process by which drug is dissolved in a solvent (water) and is characterized by a rate (amount dissolved per unit time). In vitro dissolution testing of a tablet is very important for many reasons: It guides the formulation and product development process toward optimization of dosage forms for quality control and reliability. By conducting dissolution studies in the early stages of a product's development, the formulation compositions and manufacturing parameters are also tuned and monitored about the old and newly advanced tablet. The U.S. Food and Drug Administration (FDA) allows manufacturers to examine scale-up batches of 10% of the proposed size of the actual production batch or 100,000 dosage units, whichever is greater, by performing in vitro dissolution testing to assure bioequivalence from batch to batch and processing parameters. New drug applications (NDAs) submitted to the FDA contain in vitro dissolution data generally obtained from batches that have been used in pivotal clinical and/or bioavail-

ability studies and from human studies conducted during product development. Once the specifications are established in an approved NDA, they become official (USP) specifications for all subsequent batches and bioequivalent products. The dissolution testing is also used as a tool of SUPAC (scale-up postapproval change) and variation of equipment, location, and processing factors. In addition, dissolution testing is used as a tool to examine the short- and long-term stability of dosage forms. Release mechanism and parameters which change the dissolution are also studied. Most of all, one of main goals of in vitro dissolution testing is to provide reasonable prediction and correlation with the product's in vivo bioavailability. Differentiations in the formulations and other related variables may cause deviations from in vivo bioavailability data.

A system has been developed which relates combinations of a drug's solubility (high or low) and its intestinal permeability (high or low) as a possible basis for predicting the likelihood of achieving a successful in vivo–vitro correlation (IVIVC). The four classes based on BCS are (I): high solubility and high permeability, (II): low solubility and high permeability, (III): high solubility and low permeability, and (IV): low solubility and low permeability. In class I, dissolution testing can be used as a prognostic tool to predict in vivo bioavailability.

Equations Many dissolution equations are well described in the text. Most of the equation are based on the well-known Fick's law. Figure 16 shows a diagram of the concentration gradient between the matrix tablet and bulk fluid for dissolution.

From these gradient situations, the well-known Noyes–Whitney equation is given as

$$\frac{dc}{dt} = \frac{DAK}{Vh}(C_s - C_t)$$

where dc/dt = rate of drug dissolution, where $dQ/dt = V dc/dt$

V = volume of dissolution fluid

D = diffusion rate constant

A = surface area of dosage forms

C_s = concentration of drug in stagnant layer

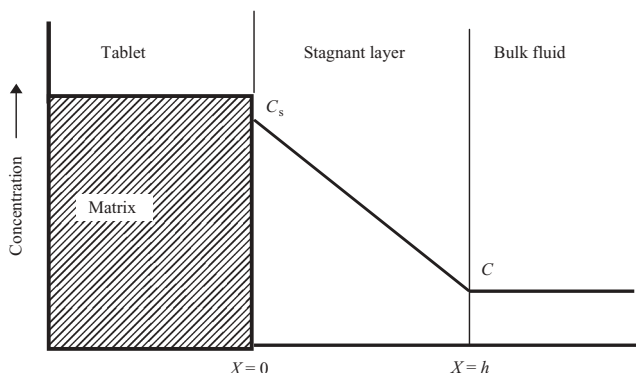


FIGURE 16 Concentration gradient from the tablet between matrix and bulk fluid for dissolution. C_s , drug solubility; C , uniform concentration; h , thickness of stagnant film; X = diffusional path length.

C_t = concentration of drug in bulk fluid at given time

K = partition coefficient

h = thickness of stagnant layer

If the bulk volume is large and the concentration of drug in the fluid is much lower than the drug solubility ($C_s \gg C_t$), it is regarded as a sink condition. In this case, the equation is much simpler and the dissolution behaviors continuously occur because the chemical potential ($C_s - C_t$) approximates drug solubility (C_s).

In a matrix tablet, the following Higuchi equations are given depending on the polymeric structures of the homogenous and porous matrix [20]:

$$Q = \begin{cases} [D(2A - C_s)C_s t]^{1/2} & \text{for homogenous matrix} \\ [D\varepsilon(2A - \varepsilon C_s)C_s t]^{1/2}/\tau & \text{for porous matrix} \end{cases}$$

In the dissolution of granular powders, the Hixson–Crowell equation is also established as

$$Q_0^{1/3} - Q^{1/3} = kt \quad \text{for granular powders}$$

Testing Method In addition to formulation and manufacturing controls, the method of dissolution testing also must be controlled to minimize important variables such as paddle rotational speed, vibration, and disturbances by sampling probes. The USP includes seven apparatus designs for drug release and dissolution testing of immediate-release oral dosage forms, extended-release products, enteric-coated products, and transdermal drug delivery devices:

Apparatus I: rotating basket method, 25–150 rpm (100 rpm)

Apparatus II: rotating paddle method, 25–150 rpm (50 rpm)

Apparatus III: reciprocating cylinder method, inner tube (5–40 dips/min), outer tube (300 mL)

Apparatus IV: flow-through method: 4–16 mL/min

Apparatus V: paddle over disc

Apparatus VI: cylinder method

Apparatus VII: reciprocating holder method

Detailed guidelines for dissolution testing are described in monographs of many pharmacopeias. The USP apparatus I and USP apparatus II are used principally for tablet dissolution testing. In USP apparatus I, the dosage unit is placed inside the basket. In USP apparatus II, the dosage unit is placed on the bottom in the vessel. In each test, a volume of the dissolution medium (500–900 mL in general) is placed in the vessel and allowed to come to $37 \pm 0.5^\circ\text{C}$. Then the stirrer is rotated at the specified speed (50–200 rpm). The samples of the medium are withdrawn for analysis of the proportion of drug dissolved. The tablet or capsule must meet the stated monograph requirement for rate of dissolution. For example, “not less than 85% of the labeled amount is dissolved in 30 minutes in case of immediate release tablet.” In a floating tablet, the sinker can be used in the paddle method.

Variables Affecting Dissolution In general, the dissolution profiles are highly dependent on the physicochemical properties, formulation, processing parameters, and testing conditions [2]. The physicochemical properties include particle size, surface area, crystal habit and polymorphism, solubility, molecular size, salt formation, pK_a , hydration, wetting, and surface tension. Physical factors such as viscosity, density, flocculation, and agglomeration are also considered. The formulation factors are also of importance. The amount and type of excipients and type of dosage forms play a key role in modifying dissolution behaviors. For example, Figure 17 gives the effect of lubricant and its mixing time on the dissolution rate of drugs. The presence of lubricant and its mixing time significantly changed tablet dissolution [31]. For poorly soluble drug, numerous pharmaceutical methods have been utilized to increase the dissolution rate of drug, including micronization, amorphous crystallization, spray drying, inclusion complex, microemulsion, and solid dispersion.

The processing parameters in the tablet preparation also change the dissolution, including temperature, mixing, milling, rotation speed, solvent, hardness, and surface area. The testing conditions are also important in modifying the dissolution of tablet. Therefore, the testing conditions are well defined by the regulations in the many pharmacopeias. The testing conditions include pH of the fluid, temperature, ionic strength, common ion effect, type of apparatus, rotation speed, volume size of dissolution fluid, analytical conditions, aeration, sample treatment, and mainly composition of dissolution media. Table 17 provides some of the media compositions suggested for in vitro dissolution testing of the tablet. These modified dissolution media can be used to achieve dissolution of drug under simulated in vivo conditions.

In Vitro–In Vivo Correlation In vitro dissolution testing can provide a reasonable prediction of the product's in vivo bioavailability. For a high-solubility and high-permeability drug (class I), an IVIVC may be expected if the dissolution rate is slower than the rate of gastric emptying (the rate-limiting factor). In a low-solubility and high-permeability drug, drug dissolution may be the rate-limiting step for drug absorption and an IVIVC may be expected. In a high-solubility and low-

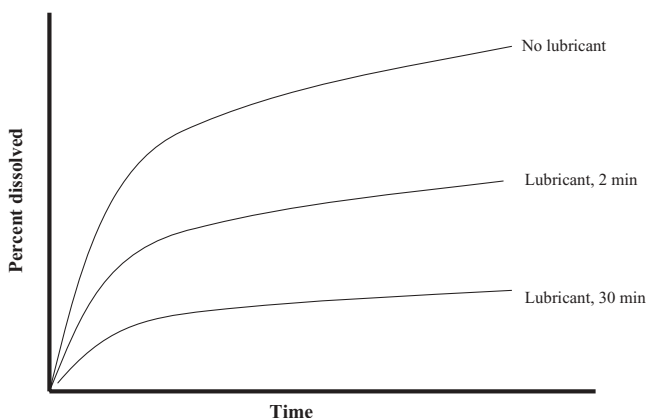


FIGURE 17 Effect of lubricant and its mixing time on dissolution rate of drugs.

TABLE 17 Suggested Media Compositions for In Vitro Dissolution Testing

Medium Type	Codes	Dissolution compositions
Water	W	Purified water
Gastric fluid (pH 1.2)	SGF	HCl–NaCl buffer
	SGF/TW	HCl–NaCl buffer/Tween 80 (1%)
	SGF/SLS	HCl–NaCl buffer/sodium lauryl sulfate (1%)
	SGF/PEP	HCl–NaCl buffer/pepsin (0.32%)
Intestinal fluid (pH 6.8)	SIF	KH ₂ PO ₄ buffer
	SIF/TW	KH ₂ PO ₄ buffer/Tween 80 (1%)
	SIF/SLS	KH ₂ PO ₄ buffer/sodium lauryl sulfate (1%)
	SIF/Pan	KH ₂ PO ₄ buffer/pancreatin (1%)
	SIF/fasted	0.2 M KH ₂ PO ₄ buffer (3.9 g)/3 mM Na-taurocholate, 75 mM lecithin/KCl (7.7 g)/NaOH (qs)/water (qs)
Intestinal fluid (pH 5.0)	SIF/fed	Acetic acid (8.65 g)/15 mM Na-taurocholate/3.75 mM, lecithin/ KCl (15.2 g)/NaOH (qs)/water (qs)

permeability drug, permeability is the rate-controlling step and only a limited IVIVC may be possible. In a drug with low solubility and low permeability, significant problems would be likely for oral drug delivery.

However, the in vivo GI condition is very complicated in terms of complex physiology and absorption process and is not simulated by the simple in vitro dissolution conditions [32]. Moreover, in vivo conditions are also complicated by food composition, type and composition of dosage formulations, relative rates of permeation, GI transit time, site of absorption, complexity of GI fluids such as pH, enzymes, bile and mucin, rate and capacity of metabolism by intestinal and hepatic enzymes, ethical difference, and patient conditions such as mood, disease, bed rest, and fasting volume of fluid given. For these reasons, in vitro dissolution is not always correlated with in vivo absorption, especially low-soluble and low-bioavailable drugs. To use dissolution testing as a prognostic tool for in vivo bioavailability, the dissolution fluid is simulated with in vivo GI condition as possible, compromising the biorelevant composition of dissolution fluid (see Table 17), gradient pH, proper stirring rate, and addition of lipid, enzyme, and surfactants.

For bioequivalence, dissolution profiles of two tablets are often compared. In this case, the difference factor and similarity factor are considered, defined by the equations

$$f_1 = \frac{\sum |R_t - T_t|}{\sum R_t} \times 100$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where R_t and T_t are the cumulative percents dissolved at each of the selected n time points.

The difference factor f_1 is proportional to the average difference between the two profiles while the similarity factor f_2 is inversely proportional to the average squared difference between the two profiles and measures the closeness between the two profiles. The two dissolution profiles are identical if $f_2 = 100$. An average difference of 10% at all measured time points results in a f_2 value of 50. The FDA guideline states that f_2 values of 50–100 indicate similarity between two dissolution profiles.

6.1.5.3 Weight Variation

With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measured to help ensure that the tablet contains the proper amount of drug. The quantity of fill placed in the die of a tableting press determines the weight of the resulting tablet. The volume of fill is adjusted to yield tablets of desired weight and content. The depth of fill in the tablet die must be adjusted to hold a predetermined volume of powder or granulation. Each tablet weight should be calculated if the amount of drug and other excipients such as diluent, disintegrant, and binder are decided.

During production, sample tablets are periodically removed for visual inspection and automated physical measurement known as in-process control (IPC). The USP provides some guidelines for weight variation. In the test, 10 uncoated tablets are weighed individually and the average weight is calculated. The tablets are assayed and the content of active ingredient in each of the 10 tablets is calculated assuming homogeneous drug distribution.

6.1.5.4 Hardness or Breaking Strength

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging, and shipping. Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance while immediate-release tablets should readily disintegrate in the stomach as quick possible. For this reason, the relationship of harness to tablet disintegration and drug dissolution has been described.

Tablet hardness has been defined as the force required to break a tablet in a diametric compression test. To perform this test, a tablet is placed between two anvils, and the crushing strength that just causes the tablet to break is recorded. Hardness is thus sometimes termed the tablet crushing strength. It is not unusual for a tableting press to exert as little as 3000lb and as much as 40,000lb of force in the production of tablets. Generally, the greater the pressure applied, the harder the tablets, although the formulation composition and manufacturing process may also change tablet hardness. In general, tablets should be sufficiently hard to resist breaking during normal handling or transportation but have no problem in disintegrating and/or dissolving after swallowing.

The hardness of a tablet, like its thickness, is a function of the die fill and compression force. At a constant die fill, the hardness values increase and thickness decreases as additional compression force is applied. This relationship holds up to a maximum value for hardness and a minimum value for thickness beyond which increases in pressure cause the tablet to laminate or cap, thus destroying the integrity of the tablet. At a constant compression force (fixed distance between upper

and lower punches), hardness increases with increasing die fills and decreases with lower die fills. The amount and mixing time of lubricants and excipients can affect tablet hardness. Large tablets require a greater force to cause fracture and are therefore “harder” than small tablets.

Special dedicated hardness testers or multifunctional systems are used to measure the degree of force (in kilograms, pounds, or arbitrary units) required to break a tablet. Devices to test tablet hardness include the Monsanto tester, the Strong-Cobb tester, the Pfizer tester, the Erweka tester, and the Schleuniger tester. A force of about 4 kg is considered the minimum requirement for a satisfactory tablet. Multifunctional automated equipment can determine tablet weight, hardness, thickness, and diameter. Unfortunately, these testers do not produce uniform results for the same tablet due to operator variation, lack of calibration, spring fatigue, and manufacturer variation.

6.1.5.5 Friability

Tablet hardness is not an absolute indicator of tablet strength since some formulations, when compressed into very hard tablets, tend to “cap” on attrition, losing their crown portions. Another measure of a tablet’s strength is tablet friability. More powders, chips, and fragments can be produced during friability test if the tablet lacks proper strength and is manufactured in dirty processes during coating and packaging. The high friability causes lacks of elegance and consumer acceptance and even weight variation or content uniformity problems.

A tablet’s durability may be determined using friability tester like Varian Friabilator testing apparatus. This apparatus determines the tablet’s friability, or its tendency to crumble, by allowing it to roll and fall within the rotating apparatus. Normally, a preweighed tablet sample is placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Any loss in weight is determined. Resistance to loss of weight indicates the tablet’s ability to withstand abrasion in handling, packaging, coating, and shipment. Compressed tablets that lose a maximum of not more than 0.5–1% of their weight are generally considered acceptable [3].

6.1.5.6 Content Uniformity

Tablet weight cannot be used as a potency indicator of its potency, except perhaps when the active ingredient is 90–95% of the total tablet weight. In tablets with smaller dosages, a good weight variation does not ensure good content uniformity, but a large weight variation precludes good content uniformity. The weight variation test would be a satisfactory method of determining the drug content uniformity of tablets. The content uniformity of the tablet is more important since the potency of tablets is expressed on labels in terms of grams, milligrams, or micrograms. The content uniformity of tablets can be varied by three factors: (1) nonuniform distribution of the drug substance throughout the powder mixture or granulation, (2) segregation of the powder mixture or granulation during the various manufacturing processes, and (3) tablet weight variation.

By the USP method, 10 dosage units are individually assayed for their content uniformity according to the assay method described in the individual monograph.

The requirements for content uniformity are met if the amount of active ingredient in each dosage unit lies within the range of 85–115% of the label claim and the relative standard deviation is less than 6.0%. If one or more dosage units do not meet these criteria, additional tests as prescribed in the USP are required. Official compendia or other standards provide an acceptable potency range around the label potency. For highly potent, low-dose drugs such as digoxin, this range is usually not less than 90% and not more than 110% of the labeled amount. For most other larger dose drugs in tablet form, the official potency range that is permitted is not less than 95% and not more than 105% of the labeled amount.

6.1.5.7 Tablet Thickness

At a constant compressive load, tablet thickness varies with changes in die fill, particle size distribution and packing of the particle mix being compressed, and tablet weight, while with a constant die fill, thickness varies with variations in compression forces. The thickness of individual tablets may be measured with a micrometer, which permits accurate measurement and provides information on the variation between tablets. Other techniques employed in production control involve placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. Tablet thickness should be controlled within $\pm 5\%$ variation of a standard value. Any variation in tablet thickness within a particular lot of tablets or between manufacturer's lots is not appropriate for consumer acceptance of the product. In addition, tablet thickness must be also controlled to facilitate packaging.

6.1.5.8 Tablet Shape and Size

The shape of the tablet alone can influence the choice of tableting machine used. Figure 18 shows some representative tablet shapes. The size, shape, and thickness

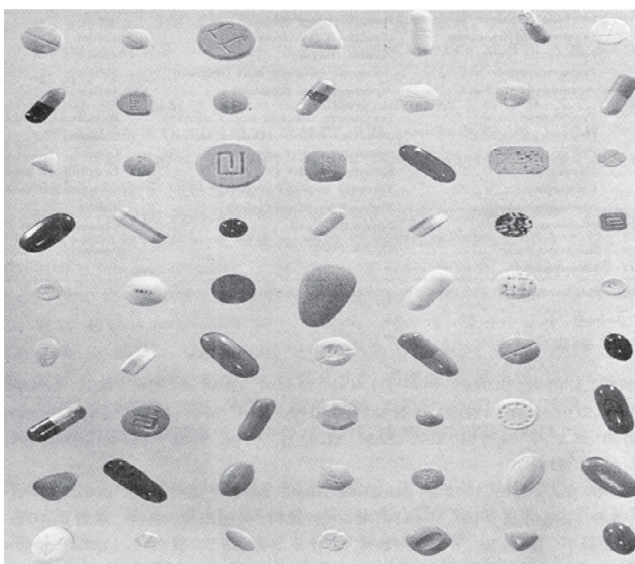


FIGURE 18 Example tablet shapes.

are very changeable. Shaped tablets requiring slotted and sophisticated punches must be run at slower speeds to avoid manufacturing disorder as compared with round tablets using conventional punches. Because of the nonuniform forces involved during compression, the more convex the tablet surface, the more likely it is to cause capping or laminating problems. The more complicated shaped tablet requires the use of a slower tableting machine or one with precompression capabilities. The size and shape of the tablet are governed by the choice of tableting machine, the best particle size for the granulation, production lot sizes, and the best type of tablet processing, packaging operation, and cost to produce the tablet.

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